EXPIRATORY MUSCLE STRENGTH TRAINING IN INDIVIDUALS WITH MULTIPLE SCLEROSIS AND HEALTHY CONTROLS

By

TONI CHIARA

A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

2003

DEDICATION

To those who have struggled due to physical, emotional, or learning disabilities do not give up your dream. There may be a bend in the road, but as in the poem "Do not Quit" - rest a while if you must, but do not quit.

ACKNOWLEDGEMENTS

Thank you so very much to A. Daniel Martin, PhD., P.T., my dissertation committee chair – I have not been the easiest student to guide through this process – you may have had your doubts a couple of times – but you did not give me the boot. Thank you for sharing your knowledge and expertise. Thank you to Drs Don Bolser, Paul Davenport, Christine Sapienza, and Orit Shechtman, my committee members, for taking the time to share your knowledge and expertise.

Thanks to my mom – though you first said I was a glutton for punishment – you have encouraged and stood behind my dream. To my dad, my brothers, Mike and Jerry, thanks for keeping an eye from beyond. Thanks to my brothers, Peter and Robert, and my sister, Claudette – though you suggested many a time for me to stop this education nonsense – you have hung in with me.

Thanks to J Carlos JR., who gave me the chance to follow my dream years before starting this phase of the journey. Thanks to those who were here at the start of this journey, but could not be here for the finish – PJ Nagy and Sister MC Norton.

TABLE OF CONTENTS

Abstract of Dissertation Presented to the Graduate School
of the University of Florida in Partial Fulfillment of
the Requirements for the Degree of Doctor of Philosophy

EXPIRATORY MUSCLE STRENGTH TRAINING IN INDIVIDUALS WITH MULTIPLE SCLEROSIS AND HEALTHY CONTROLS

By

Toni Chiara

December, 2003

Chair: A. Daniel Martin III,
Major Department: Physical Therapy

Multiple sclerosis (MS), a demyelinating disease of the central nervous system (CNS), may result in weakness of the respiratory muscles. Weakness of the expiratory muscles may impair effectiveness of cough and the ability to speak. No study has examined expiratory strength training in individuals with mild to moderate disability because of their MS. Previous studies have examined only those with severe disability. **Purpose:** The purpose of this project was to examine the effect of pressure-threshold strength training of the expiratory muscles of respiration on cough effectiveness and speech loudness and prolongation. **Subjects**: Seventeen individuals with MS and 14

healthy controls used a pressure-threshold device (Threshold PEP) to strength train their expiratory muscles. **Procedures**: Subjects trained 5 days per week for 8 weeks followed by 4 weeks of no training. **Results:** Maximal expiratory pressure (MEP), the measurement of expiratory muscle strength, was less than normal for the persons with MS (PwMS) and was significantly less than the healthy controls (H) prior to and after training. PwMS and H subjects significantly improved MEP ($p < 0.0001$) following training. Significant change in pulmonary function was found for forced vital capacity and peak expiratory flow ($p < 0.05$). Significant difference was found in the rise time of maximal voluntary cough in individuals with MS and the healthy subjects. Cough volume acceleration (CVA) was less in PwMS compared to the healthy controls each time it was evaluated. Significant differences between the individuals with MS and the healthy subjects were found in speech acoustic components, i.e., vowel prolongation and words per minute, and aerodynamic component, i.e., phonation at normal and loud sound pressure level (SPL). **Discussion**: Minimal changes found in cough effectiveness may have occurred secondary to lack of training specificity. Additionally, the components of cough measured may not have been adequate to assess the affect of expiratory muscle strength training on maximal voluntary cough. Subjects stated they could talk louder and though no PwMS reported problems with shortness of breath (SOB) prior to training, PwMS reported easier breathing after training. **Conclusions:** Pressure threshold strength training of the expiratory muscles benefits PwMS by increasing MEP, which improves vocalization. However, based on the measurements of effectiveness of cough used in the current study, pressure threshold strength training does not improve maximal voluntary cough.

CHAPTER 1
INTRODUCTION

Respiratory impairment in multiple sclerosis (MS) has been recognized and studied only during the last few decades, with most studies reporting a low incidence of respiratory dysfunction in persons with MS (PwMS) (17). Respiratory impairment has generally been reported as occurring late in the disease and is a principle cause of death (110). Several forms of ventilatory dysfunction in MS occur: 1) paralysis of voluntary respiration, 2) paralysis of autonomic respiration, 3) diaphragmatic paralysis (unilateral or bilateral), 4) apneustic breathing preserved, 5) paroxysmal hyperventilation, 6) obstructive sleep apnea, and 7) neurogenic pulmonary edema (3, 12, 15, 17, 21, 51, 73, 87, 143, 177). A common thread in these problems is respiratory muscle weakness. In PwMS, either group of respiratory muscles, inspiratory and/or expiratory, may be impaired. Respiratory muscle weakness, particularly in the expiratory muscles, leads to a restrictive pulmonary disease in which cough and production of speech may be impaired. Strengthening respiratory muscles may improve respiratory function, efficiency of one's cough, and speech.

Since the late 1970's, investigators have examined the feasibility of strengthening the inspiratory and/or the expiratory muscles in individuals with and without disease (3, 12, 15, 17, 21, 51, 52, 73, 87, 110, 131, 143, 168, 177, 189). Five studies have examined the feasibility of strengthening the respiratory muscles in PwMS (52, 83, 131, 168, 189).

Two studies have used expiratory muscle strength training (EMST) (52, 168), two trained both the expiratory and inspiratory muscles (131, 189), and one used inspiratory muscle strength training (IMST) (83). Expiratory muscle weakness can reduce the strength of maximal voluntary and reflexive cough. Only two have examined the change in respiratory muscle strength in relation to clinical or functional skills (52). Gosselink et al, (52) examined EMST in relation to it's effect on coughing in PwMS. Klefbeck and Nedjad (83) examined the gains in inspiratory muscle strength in comparison to fatigue level, functional level, i.e., ability to perform activities of daily living (ADL), and respiratory function, but not cough or vocalization.

The respiratory pump mechanism provides the airflow and subglottic pressure necessary for the generation of sound in the larynx (20, 68, 138, 156). Expiratory muscle weakness limits the production of speech as speaking is achieved by airflow through the glottis to produce audible waves. The column of air is generated by the contraction of the expiratory muscles. Therefore, in the presence of decreased expiratory muscles strength, an insufficient airflow may result, diminishing vocal production. No study has examined the relationship between increased inspiratory and/or expiratory muscle strength and vocalization, e.g., improved loudness of vocalization in PwMS.

Impaired cough and vocalization are more apparent in PwMS late in the disease process (82, 94, 95, 131, 168). However, respiratory muscle weakness is known to be present early in the disease (168). Strengthening the respiratory muscles early in the disease may permit PwMS to retain a normal cough, possibly limiting the occurrence of respiratory infections and maintaining adequate loudness during vocalization, such that both factors may lead to improved quality of life. Reducing the risk of respiratory

infection and maintaining the ability to communicate may reduce economic and emotional burden on PwMS.

Quantitative Evidence

Previous studies examining either inspiratory and/or expiratory muscle strengthening in PwMS have provided limited quantitative evidence as to the functional benefit of increased strength. Gosselink et al, (52) used the Index of Pulmonary Dysfunction (IPD) which was developed by Smeltzer and associates (170). The IPD is composed of subjective and objective measurements to examine the relationship between expiratory muscle strength and coughing. However, only one of the four tasks of the IPD, counting out loud following a maximal inhalation, could be considered an objective assessment, while the other tasks are subjective. Smeltzer et al, (170) in developing the IPD to examine respiratory function and cough in PwMS in a clinical setting, did not compare improved MEP and/or MIP to changes in the IPD. Smeltzer et al, (168) did not use the IPD to compare change in expiratory muscle strength to change in cough. These investigators did recommend that future studies investigating respiratory muscle strength in PwMS should examine the relationship of muscle strength and cough (168). Studies by Olgiati et al, (131) and Wiens et al, (189) examining respiratory muscle strength training in PwMS did not relate changes in respiratory muscle strength to any functional changes. As only one study has compared gains in respiratory muscle strength to cough and no study has examined the effect of training expiratory muscle on speech in individuals with MS, a study is warranted that examines the relationship of expiratory muscle strength to cough and vocalization.

Due to the lack of objective measurement and limited quantitative evidence about the functional/clinical relevance of improved respiratory muscle strength as pertains to PwMS this project was undertaken. Participants in previous inspiratory and/or expiratory muscle training investigations in PwMS had significant disability as measured by the Expanded Disability Status Scale (EDSS) (85). The EDSS is a twenty step scale of disability ranging from '0' normal neurologic examination to '10' death due to MS (see Appendix A). The EDSS scores reported in three of the studies ranged from 7 to 9.5 (52, 168, 189). No study has assessed the level of expiratory muscle strength in PwMS at lower levels of disability (≤ 6.50, upper level of moderate disability), i.e., early in the disease process, nor objectively associated expiratory muscle strength to cough and loudness of vocalization. The current investigation examined the effect of expiratory muscle strengthening in PwMS who have mild (0 to 3) to moderate (3.5 to 6.5) disability on cough and vocalization.

Expiratory Muscle Strengthening and Clinical Relevance

Cough

Cough is an airway protection process. Cough, a sign and/or symptom in many disease processes, can occur voluntarily or reflexively. Coughing is a maneuver in which "respired gas acts as a fluid coupling which transmits energy from the respiratory muscles to other sites in the respiratory system" (97). Cough is a primary airway defense mechanism along with the mucociliary mechanism. However, the effectiveness of cough is dependent on the neural control influencing the strength and endurance of expiratory muscles. Impaired cough increases the risk of respiratory infections and respiratory failure due to aspiration.

Theoretically, strengthening the expiratory muscles should enhance coughing ability. PwMS who have expiratory muscle weakness may not acknowledge or display a dysfunctional cough. A quantitative assessment of expiratory muscle strength and components of cough (e.g., flow, pressure, and volume) is needed due to the lack of objective appraisal of expiratory muscle strength training influence on cough.

Little to no evidence about the feasibility of muscle training of either the inspiratory or the expiratory muscle to improve coughing existed prior to the mid-1980's (97). Of the five studies that have examined respiratory muscle strengthening in PwMS, only one has related change in respiratory muscle strength to change in an individual's ability to cough (52). However, the assessment was primarily subjective with minimal objective measures. A recent investigation, examining EMST in healthy subjects, reported no improvement in maximal flow or rise time. However, the investigator reported that following EMST at four and eight weeks of detraining the compression time of cough was shorter than prior to training (5).

Vocalization

A second sign and/or symptom that may occur in the presence of expiratory muscle weakness is impaired vocalization, particularly the inability to increase the loudness of the voice (66, 88). Production of sound is dependent on several factors: 1) approximation of the vocal folds, 2) proper amount of tension and elongation of the vocal folds, and 3) airflow from the lungs, generated by lung pressure (20). Having the ability to produce the required flow of air from the lungs requires there to be a sufficient quantity of air in the lungs. The inspiratory muscles, expanding the chest cavity, and the laryngeal muscles controlling abduction of the vocal folds, influence inward flow of air.

The expiratory muscles and the laryngeal muscles adducting the vocal folds influence the outward flow of air, from the lung. Inadequate expiratory muscle strength diminishes the outward flow of air, impairing the skill to change the loudness of vocalization (20). Limited data exist as to the effect of expiratory muscle strength on an individual's ability to change loudness of voice. A recent investigation has shown that EMST can improve one's ability to project one's voice at a louder level with diminished strain on the vocal folds (69).

Completed Investigation

The current investigation examined the effect of EMST on cough in PwMS and healthy individuals. Healthy individuals were exposed to the same treatment as the PwMS to serve as an age and gender matched control group. A second area of examination was the effect of EMST on individuals' speech, specifically the ability to change loudness of voice and prolong vocalization.

Respiratory muscle strength training in PwMS has improved respiratory muscle strength (52, 83, 131, 168) and has not improved respiratory muscle strength (189). However some questions remain to be answered. For example, does increasing expiratory muscle strength, which may improve the effectiveness of one's cough and/or ability to increase the loudness of one's voice, warrant further investigation in this population? Is there a difference in the ability to improve expiratory muscle strength, loudness of voice and/or functional cough in individuals with different levels of disability (i.e., mild compared to moderate disability) due to MS?

Numerous articles document the need for continued training in skeletal muscle to maintain strength and endurance gains. Two studies examining IMST or EMST in

individuals with MS have involved detraining periods of 1 month and 3 months, respectively, with reassessment with follow-up (52, 83). As yet only one study has investigated the effect of detraining following EMST on cough and speech in healthy subjects (5). If improvement in cough, loudness of vocalization and prolongation of vocalization occurs with training, will it be maintained when the training has been stopped? Will the gains be lost and how quickly does this happen?

Hypothesis and Specific Aims

We hypothesized that increased strength of the expiratory muscles would take place due to the pressure-threshold load training. The increased expiratory strength would improve the pressure generation during coughing, facilitating a stronger cough. Additionally, the increased expiratory strength would improve the ability to increase loudness of voice and prolong vocalization.

Questions addressed in this project were:

1) Will PwMS, with mild to moderate disability, improve their expiratory muscle strength assessed as increased maximal expiratory pressure (MEP)?

2) Will increased expiratory muscle strength improve maximal voluntary cough in healthy subjects and in PwMS?

3) Will increased expiratory muscle strength translate to improvement in vocal loudness and speech duration in healthy subjects and in PwMS?

4) Will increased expiratory muscle strength translate to improvement in pulmonary function and airway resistance in healthy subjects and in PwMS?

5) Will detraining occur after the termination of the treatment program, resulting in a greater detraining effect in the PwMS than the healthy controls?

CHAPTER 2
LITERATURE REVIEW

Respiratory Muscle

Respiratory muscles are skeletal muscle, which comprise the motor end organs of the neural pathways controlling ventilation. Respiratory musculature is affected in many neurological and neuromuscular diseases, such that any disorder, which affects skeletal muscle, may impair respiratory musculature. A great majority of neurological and neuromuscular disease morbidity and mortality is caused by respiratory muscle weakness (180). Any disease which abnormally affects the peripheral chemoreceptors, central chemoreceptors, and/or the respiratory neurons of the pons and medulla may affect respiratory muscle strength and endurance (176). Lesions within the central nervous system (CNS) and peripheral nervous system (PNS), including the motor and/or sensory cortex, neural pathways, spinal nerves, peripheral nerves, myoneural junctions, sarcolemma t-tubule system, or the muscle fiber, may result in respiratory muscle weakness. Respiratory muscle involvement depends on a multitude of factors, in particular the type of neurological or neuromuscular disease and the distribution rather than the degree of general muscle weakness (182).

An important reported clinical finding is that large ranges of respiratory pressures, from normal to very abnormal, can be found in patients with stable chronic neuromuscular disorders with relatively well preserved general muscle strength (6). Additionally,

early in the disease, the maximal static respiratory pressures, assessed as maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP), can be abnormal even though the results of spirometry are normal (11). Respiratory muscle weakness may go undetected until the precipitation of ventilatory failure by aspiration pneumonia or the development of cor pulmonale. This arises in part because impaired skeletal muscle function prevents patients from exceeding their limited ventilatory capacity and also because respiratory muscle weakness often is greater than the level of general muscle weakness (179, 182). Late detection of respiratory muscle weakness may occur due to much greater strength and endurance reserve of the respiratory musculature than in the general skeletal musculature.

Respiratory musculature includes the inspiratory muscles (diaphragm, external intercostals), the accessory muscles of the neck (scalenes, sternomastoid), and the expiratory muscles (internal intercostals, abdominal muscles). Respiratory, either inspiratory and/or expiratory, musculature weakness may impair physical activity ability (23, 59). But it is weakness of the expiratory muscles that compromises airway defense mechanisms due to ineffective generation of a column of air and airway compression to remove mucus and foreign objects, i.e., ineffective cough, that heightens the probability of morbidity and mortality due to respiratory complications (96-98). Additionally, impaired vocalization due to weakened expiratory musculature negatively influences an individual's quality of life due to decreased communication hampering one's ability to maintain a job and/or personal communication, such as indicating one's needs or desires. Many neurological or neuromuscular diseases have negative effects because of

respiratory muscle weakness, including the disease examined in this project, MS, which affects young adults in particular, as well as occurring in children and the elderly.

Prior to discussing the effect of respiratory muscle weakness particular to MS, a general overview of respiratory muscle weakness in neurologic and neuromuscular disease will be presented (93, 116, 118, 179). In the presentation of MS and respiratory muscle weakness, the primary discussion will be on the influence of the weakness of the expiratory muscles on physical activity, respiratory volumes, cough and vocalization.

Respiratory Muscle Weakness vs. Fatigue

Muscle weakness must be distinguished from muscle fatigue. Weakness is defined as a condition in which the capacity for a rested muscle to generate force is decreased and not reversed by rest (176), or a failure to generate an expected force (14). For the respiratory muscles this can be represented by reductions in maximum inspiratory and expiratory forces (14). Weakness may develop due to failure of neuromuscular transmission, failure of the excitation-contraction coupling, and central fatigue occurring in other skeletal muscles and the respiratory muscles (90). Additional causes include deconditioning, which decreases the size and oxidative capacity of muscle fibers, steroid myopathy, and the release of tumor necrosis factor-α during exacerbations (90). In contrast, fatigue is defined as a condition in which there is loss in the capacity for developing force and/or velocity of a muscle in response to a load, which is reversible by rest (14). Muscle contraction secondary to the application of a large respiratory load over a long period results in fatigue (90). For the respiratory muscles, the inability to sustain or maintain sufficient ventilation for normal arterial carbon dioxide (CO_2) tension or to maintain transdiaphragmatic pressure with loads can indicate fatigue (14). Except among

very strenuous conditions such as marathon running or exhaustive exercise, respiratory muscle fatigue does not typically occur in normal individuals (90).

Though respiratory muscle weakness is the principal issue of discussion, further differentiation of fatigue from weakness is warranted as both may occur due to lesions involving many of the same structures. Respiratory muscle fatigue may be of central or peripheral origin depending upon whether motor neurons generate action potentials. Central fatigue can be motivational or due to a genuine reduction in central motor drive. Force generated by voluntary effort that is less than that achieved with electrical stimulation characterizes central fatigue. This result is due to a failure to sustain the number and/or stimulation frequency of motor units (14). Central fatigue may represent an important adaptive mechanism that avoids the adverse effects of prolonged forceful contractions. Central fatigue affects the respiratory muscles of PwMS (90). Peripheral fatigue is characterized by force loss with the same stimulation frequency. Interruption of peripheral nervous transmission to the muscles or failure of excitation-contraction coupling can cause peripheral fatigue. Peripheral fatigue may also be due to failure of the contractile machinery itself, due to hypercapnia, hypoxemia, drugs and electrolyte disturbance (176). Muscle fatigue also depends on the rate of stimulation that causes the fatigue. Peripheral fatigue is further separated into high- and low frequency (14, 93). High-frequency fatigue is generally attributed to alterations in t-tubule excitability such that forces generated at higher rates are disproportionately affected. High-frequency fatigue is thought to be caused by impaired neuromuscular transmission and /or propagation of the muscle action potential (14). High frequency fatigue recovers rapidly (93). Low-frequency fatigue may arise from failure of excitation-contraction coupling

due to inadequate release of calcium or to alteration in actomyosin adenosine triphosphatase activity. Force is selectively reduced at low frequencies, whereas maximum force still can be generated by high frequency stimulus. Low frequency fatigue is slower to recover and may be difficult to distinguish from muscle weakness. Low frequency fatigue of the diaphragm has been demonstrated after inspiratory muscle loading, after repeated voluntary contractions and after global endurance exercise in healthy subjects (93).

Consequences of Respiratory Muscle Weakness and/or Fatigue

Respiratory muscle weakness and/or fatigue can contribute to dyspnea, reduced exercise tolerance, nocturnal desaturation, prolonged weaning from mechanical ventilation, increased occurrence of respiratory infections, hypoxemia, widening of the alveolar-arterial gradient, and respiratory failure (14, 93, 116, 119, 176, 179, 188). Hypercapnia is minimal during the early stages of respiratory muscle weakness but increases as strength falls to 30% of predicted (93, 116, 179). Depending on the disease entity, the ventilatory response to hypercapnia is normal or decreased (179).

Patients with respiratory muscle weakness typically present with a "restrictive" pattern on pulmonary function testing:1) markedly decreased vital capacity (VC) (40 to 70 % of predicted), 2) reduced total lung capacity (TLC) and functional residual capacity (FRC), and 3) relatively normal residual volume (RV) and ratio of forced expiratory volume in the first second (FEV_1) to VC (FEV_1/VC) (179). Tachypnea, a rapid shallow pattern of breathing (93, 116, 179) and infrequent sighs (179), may result from respiratory muscle weakness.

Weakness of the expiratory muscles is associated with an impaired ability to cough (93, 116) (23). Presence of wasting and fasciculation of the intercostal and accessory muscles of respiration suggests weakness (93). Wasting of the accessory muscles and/or weakness of the intercostal muscles in association with a pliant rib cage and spine may result in such deformities as ankylosis of the costosternal and thoracovertebral joints (179), pectus excavatum, or kyphoscoliosis and impaired respiratory function (93). Acute weakness does not affect lung compliance. However, prolonged weakness may cause lung stiffness as well as eventual chest stiffness (116). Chest wall compliance is decreased to about 70% of the normal value, primarily because of increased stiffness of the rib cage due to fibrous replacement of muscle tissue (179, 182) (23). Reduced pulmonary compliance (116, 179) modifies the intrinsic properties of the airway, which in and of themselves are not affected by weakness (116). Either microatelectasis or generalized alterations in alveolar elastic properties produces the low compliance (48). Involvement of the pharyngeal and laryngeal muscles can also be present resulting in weakness of the voice, dysphagia, or aspiration. Bilateral diaphragmatic paralysis may result in extreme orthopnea and abnormally large (>25%) postural fall in vital capacity (93, 116). Inspiratory muscle weakness, predominantly diaphragm, may result in impaired tracheobronchial mucociliary clearance (116, 119). Paradoxical inward motion of the chest wall occurs during inspiration when there is weakness of extra-diaphragmatic muscles. Severe weakness of the diaphragm results in paradoxical inward instead of outward movement of the abdominal wall during inspiration (116).

Weakness of the principle inspiratory muscle, the diaphragm, may be in the form of either unilateral or bilateral paralysis. Minimal complications occur in unilateral paralysis. However, in patients with bilateral paralysis, breathless on exertion is usually a prominent symptom. Severe orthopnea and extreme breathlessness on entering water may occur (93, 116). Paradoxical inward movement of the abdominal muscles occurs in the supine position during inspiration in the presence of isolated diaphragm paralysis (93, 116).

Investigation of Suspected Respiratory Muscle Weakness

Various techniques are available to assess the presence and severity of respiratory muscle weakness. First, radiography by the use of X-ray or fluoroscopy shows the position of the diaphragm, i.e., elevation of unilateral or bilateral hemi-diaphragm. Unfortunately, appearance of elevation is non-specific to respiratory muscle weakness. Fluoroscopy shows paradoxical diaphragm movement during inspiration or sniffing (93). Second, lung function tests are non-specific in patients with respiratory muscle dysfunction due to influence of other non-related pathological changes in the chest wall or lung (93). Reductions occur in VC, forced vital capacity (FVC), and TLC. Whereas, changes in RV are variable, but may be elevated due to reduced expiratory muscle strength (117). FRC may be normal, or increased (93), or reduced due to loss of end-expiratory tone in the muscles that hold the chest wall out (116). Third, tests of maximum isometric force which the muscle can generate at its optimal length, that being at RV for inspiration (PImax or MIP) and TLC for expiration (PEmax or MEP), are highly influenced by the motivation and effort of the individual performing the test (93, 116). Other limitations include the individual coordination and understanding (93, 116).

The type of mouthpiece used in test equipment, tubular or flanged, may affect the performance of the subject (93). Inspiration can be done during an occluded maneuver or with a sniff maneuver (116). Fourth, maximal transdiaphragmatic pressure may be obtained using a sniff procedure during inspiration when the subject has balloons connected to pressure transducers positioned in the esophagus and the stomach (93). Fifth, measuring phrenic nerve conduction time via electrical stimulation or magnetic stimulation (93) may assess phrenic nerve function, imperative in the function of the diaphragm. Lastly, the use of cough, i.e., measuring the gastric pressure, has been described as a method to assess expiratory muscle pressure (104). Desiring to use a non-invasive technique in the acquisition of data, the completed research used maximal static maneuvers, minimizing the potential for inaccuracies by techniques discussed below in the methods section.

Laryngeal Musculature

Muscles of the larynx, which are not part of the respiratory pump, have an important role in the flow of respired gas, which acts as a hydraulic fluid to transmit energy from the respiratory muscles to other sites in the respiratory system. Activity of the laryngeal musculature permits sound production, i.e., phonation, singing, whistling, and snorting. Laryngeal musculature permits movement of material outward or inward, i.e., coughing, forced expiration, clearing one's throat, hawking, spitting, sneezing, nose-blowing, sniffling, and snuffling (97). Laryngeal musculature forming the glottis (ventricular bands or false cords) and supraglottic structures of the larynx, but not the epiglottis or the true vocal folds, are used to restrain the very high tracheal pressures encountered in coughing. The larynx has a dual role in the cough mechanism by storing

and coordinating the expiratory impulse and by reflexively increasing net expiratory muscle activity (97). Weakness of the laryngeal musculature further compromises airway defense mechanisms in the presence of weakened respiratory pump musculature, especially expiratory musculature. Change in tone of the bulbar musculature as well as change in tone of the airway smooth muscle or inflammation may result in changes of airway resistance.

Airway Resistance

Previous studies examining pulmonary function in individuals with MS have not presented data about airway resistance. Most data presented in the literature discuss airway resistance in relation to obstructive disorders. Airway resistance may occur in the presence of impaired vocal fold abduction (18). No data were found as to the effect, if any, that strengthening of the respiratory muscles might have on airway resistance in neurological disorders.

Resistance of any system is the ratio of pressure and flow. Resistance within the airways is due to the driving pressure needed to overcome frictional forces opposing a given flow in or out of the respiratory system. In the pulmonary system, airway resistance is the relationship between the pressure due to the respiratory muscles and the airway structures and the flow of air during a respiratory cycle. Airway resistance may be examined by plethysmography or oscillations. Resistance within the pulmonary system includes that from the airways, the lung tissue and the chest wall. The resistance for the lung tissue and chest wall is negligible, therefore measurement is total respiratory resistance (29). The current study used impulse (forced) oscillations (IO) to assess total respiratory resistance. A pump delivering a constant volume stroke (oscillation) at

different frequencies, administered at the mouth of a subject permits the measurement of the total respiratory resistance (Rrs) (29). DuBois and colleagues (29) reported the resistance for the conducting airways to be 1.5 cm H_2O/l/s at 1/l/s. van Noord and associates (181) reported increased airway resistance in patients with diffuse interstitial lung disease with evidence of neurological or neuromuscular involvement. Greater resistance occurred in patients with TLC of less than 80% of predicted. Impulse oscillation was sensitive to the degree of pulmonary restriction, as IO did not distinguish a small increase in airway resistance. However, in the presence of advanced restrictive disease the alterations of Rrs and reactance (Xrs) being comparable to mild obstructive disease were distinguishable (181).

Previous investigators, using frequencies ranging from 3 to 30 Hz, reported Rrs as expressed as mean ± SD ranging from 2.2 ± 0.12 to 3.2 ± 0.62 cm H_2O/l/s (78, 92). Total respiratory resistance is greater in women than in men, and is correlated to body height (78, 92, 134). More recently, Peslin et al, (134) using the higher frequencies of oscillation 10 to 30 Hz, reported the lowest resistance occurred at 20Hz with a mean Rrs of approximately 2.25 hepta-Pascals a second per liter ($hPa \cdot s \cdot l^{-1}$). Rrs was greater during expiration than inspiration. Greater expiratory resistance is attributed to smaller glottic opening during expiration and to gas convective acceleration from alveoli to mouth (134). Data are limited as to the influence of weakened expiratory muscles on total airway resistance.

Consequences of Expiratory Muscle Weakness

As indicated above, many signs and symptoms may result due to weakness of the expiratory muscles. However, two impairments are of particular interest to this current research: cough and vocalization.

Cough

Cough has two protective functions: 1) serves as part of a system of reflexes that keep foreign materials from entering the airway and 2) expels foreign material and excessive secretions from central intrathoracic airways (98). Coughing is one member of a class of respiratory maneuvers in which the respired gas acts as a fluid coupling which transmits energy from the respiratory muscles to other sites in the respiratory system (97). Peak cough flows of 160 l/min are the minimum required in adults to clear airway debris without resorting to tracheal intubation (180). The energy / force generated in a muscle during a cough is the pressure resulting in a rise in pleural pressure, which is well above pressure at the airway opening. However, in the presence of weakened expiratory muscles, alveolar pressure, pleural pressure, and the transpulmonary pressure, result in insufficient energy to move the respired gas (180). Minimal expiratory pressure for effective cough has been reported to range from 40 to 60 cm H_2O (18).

Coughing, a complex centrally-organized event that may be initiated reflexively or voluntarily, occurs due to the interaction of three elements: 1) the *controller*, that is the receptors, afferent and efferent pathways and central, 2) the *motor*, that is the musculoskeletal system for breathing, including the glottis, and 3) the *pump*, that is, the mechanical properties of lung and airways must be such as to permit the high volume flows and local flow velocities (98). Cough mechanics has two primary components:

forced expiration, which is respiratory mechanics and two-phase concurrent flow, which is fluid mechanics (98). The forced expiratory influence on cough's upper limits to expiratory flows are normally set, not by muscle strength or effort, but by a flow-limiting mechanism operating in the lung and intrathoracic airways. Narrowing of the airways during cough occurs at choke points, which prevents linear velocities from exceeding the maximal velocity at which pressure disturbances are propagated along the airways at those points (tube wave speed) (74, 98). Greater narrowing occurs when the expiratory muscle pressures exceed that needed to reach maximal expiratory flow indicating that muscle strength, though it does not set upper limits to flow or determine choke point locations, does influence cough effectiveness (97, 100). Two-phase concurrent flow refers to the flow of gas and liquid together in the same direction within a tube. Leith described four flows that may occur: bubble, slug, annular, and misty (97, 100). The most important clearance mechanism in coughing is mist flow, in which liquid droplets are suspended and cleared (98).

A cough is usually described as having three successive phases. Phase one is the 'inspiratory phase' in which a volume of air, larger than tidal volume at rest, is drawn in to the lungs (81, 97, 150). In a voluntary cough, the inspiratory volume varies depending on the expected force of the cough with greater force being generated at high lung volumes due to the lengthened expiratory muscles (150). Phase two, the 'compressive phase', the glottis is shut while thoracic and abdominal expiratory muscles contract forcefully (81, 97, 150) and the pressure in abdominal, pleural, and alveolar spaces is raised to 50-100 mmHg (97). Contraction of the respiratory muscles is in a coordinated manner, permitting intrathoracic and intrapulmonary pressures to rise to levels which are

sometimes greater than can be generated during voluntary maneuvers of maximal expiratory efforts against a closed glottis (150). After approximately 0.2 to 0.4 seconds, the glottis opens suddenly and expiratory flow begins (81, 150). Cough is possible without the compressive phase as individuals with a tracheostomy or a laryngectomy learn to "cough" effectively (97). Phase three, the 'expulsive or expiratory phase', is a sudden decompression during which a blast of air is blown out at a very high rate (81, 176); flow may exceed 12-l/sec (97). Airway pressures drop in the large central airways while air pressure continues to rise rapidly in the peripheral airways and airflow peaks rate (81, 150). With high intrathoracic pressures and falling pressures in the central airways, dynamic compression of the central airways occurs (81, 150). Graphic representation of a cough will show a 'spike' of flow on top of more sustained expiratory flow through the airways from lung parenchyma (97). Effective cough in neurological or neuromuscular disease is defined by the absence or presence of cough spikes (18). Some authors include a fourth phase, 'cessation phase ' during which the expiratory muscles relax and alveolar pressures eventually return to normal level (150).

Coughing is recognizable by its characteristic sound, reproducing the sound associated with it when the word is vocalized (150). Cough does not normally occur in healthy individuals except in response to exogenous mechanical and chemical irritants (97, 150). Normally the clearance of the respiratory tract is satisfactorily managed by other mechanisms – for example, macrophages and the mucociliary system, however when these systems fail, or when they are overloaded by foreign materials or by sections abnormal in kind or amount, coughing is a fast and powerful adjunct (97). In most

circumstances coughing is a reflex response elicited primarily by irritant stimuli to the larynx and the tracheobronchial tree (81).

Different afferents are involved in laryngeal and tracheobronchial cough. Sant'Ambrogio and coworkers (152) identified afferent endings activated by inspiratory cooling of the laryngeal lumen ("flow" receptors), by changes in laryngeal transmural pressure (pressure receptors) and by contracting laryngeal muscles and the tracheal tug ("drive" receptors). Elicitation of laryngeal cough also occurs through stimulation of irritant receptors with myelinated fibers and C-fiber receptors; it is characterized by a more pronounced inspiratory phase and a less pronounced expiratory phase with more frequent expiratory efforts (150, 152). Cough elicited in the epipharyngeal and larynx areas serves more of a preventive function to expel materials, which might otherwise be aspirated into the airway (97). Cough elicited from the tracheobronchial tree involves four types of receptors: slow adapting receptors (a regulatory role), rapidly adapting receptors (a stimulatory role), and bronchial and pulmonary C-fibers (a stimulatory role) (19, 149, 150, 152). The afferent fibers travel to the medullary centers, the principle area of neural control of cough. The sensory innervation of the lower airways includes a component whose cell bodies are in the upper thoracic dorsal root ganglia and whose fibers travel to the spinal cord with branches of the sympathetic nerves (19).

Spontaneous cough is a defense mechanism that protects the lungs against aspiration of foreign material and removes excessive airway (mostly tracheobronchial) secretions (150, 152). A weakened or dysfunctional cough may result in ineffective airway clearance, that is "A state in which an individual is unable to clear secretions or obstructions from the respiratory tract to maintain airway patency" (81). An ineffective

cough is due to failure of the cough mechanisms: 1) impaired driving system can result from decreased sensitivity of cough; 2) failed central processing due to depression by neurological illness or injury, drugs, hyperthermia, age, debility, and /or inhibition due to pain; and 3) muscular and efferent neural abnormalities (97). Recently, the strength of one's cough, i.e., the gastric pressure generated during a voluntary cough has been used to measure the strength of the expiratory muscles (104).

A series of coughs that is generally more effective than a single cough. The effectiveness, as measured by the amount of flow and tracheal cross section, is greatest in the first cough decreasing progressively with each cough (97). In the presence of weakened expiratory muscles and/or bulbar muscles diminished flow and tracheal cross section at each cough in the series further impairs the effectiveness. Cough, a symptom of many neurological or neuromuscular diseases with respiratory dysfunction, is triggered by endogenous stimuli such as mucus hypersecretion, mucosal swelling, epithelial sloughing and increase in epithelial sloughing and increase in epithelial permeability (150). The effectiveness of coughing as a clearance mechanism for the tracheobronchial tree depends on 1) the presence of a sufficiently thick mucus layer lining the airway mucosa and 2) the linear velocity of the air flowing through the airway in an expiratory direction (150, 151). Persons with neurological or neuromuscular disease have greater impairment in the second factor, airflow, due to muscle weakness that results in an ineffective cough. Vocal fold impairment may result in a longer time to reach maximum cough peak flow rate. When the vocal folds do not appose fully during the compression phase there is air leakage. The air leakage limits the rise in intrathoracic pressure and reduces dynamic airway compression (18). Ineffective airway clearance due to

dysfunctional cough precipitates aspiration pneumonia that leads to increased morbidity in individuals respiratory muscle weakness.

Variability exists in the flows, pressures, and volumes generated by healthy young adults. Pressures available during coughing are limited by strength, which varies with age, sex, and physical fitness, increasing in some athletes and decreasing with general debility. Peak air flow, i.e., the highest "instantaneous" expiratory flow near the onset of a forced expiration, values around 600 l/min (10 l/sec) have been achieved in healthy young adults (97). Peak flows, related to body size, have a normal value close to 2 vital capacities/sec. Velocities of gas flow have been estimated as reaching 25,000 cm/sec or three–quarters of the speed of sound (97). Reported lung volumes range widely from inspirations of 0.5 liters and 0.2 liters and expirations of 1.1 liters and 0.6 liters by young men and women, respectively, to inspiration and expiration of 1.7 to as much as 2.5 liters in a single cough (93).

Having an understanding of the neural structures involved in cough facilitates determining which structures are involved in the ineffective cough. Knowing involved structures may permit addressing the ineffective cough by therapeutic means. Previous writers have presented a thorough review of the neurological components and associated neurotransmitters (19, 97). Cough dysfunction seen in PwMS is discussed below.

Speech Production

Mechanical and neurological mechanisms for the production of speech will be briefly reviewed. Colton and colleagues, (20) described speech as being produced principally by the vibrating vocal folds and to a lesser degree by the movement of the articulators. Vocal folds need to be open for inhalation, but need to be brought together

or completely closed to permit phonation. Production of sound, due to the vibrating rate of the vocal folds, is dependent on proper tension and elongation of the vocal folds. Outward airflow from the lungs, necessary for the production of sound, is dependent on sufficient quantity of air in the lungs prior to vocalization. Phonation occurs as a series of alternate openings and closings of the vocal folds, regulated by the degree of tension in the vocal folds and by flow of air.

Production of sound involves two aerodynamic events. First, Bernoulli's second law of fluid mechanics, states that when there is increased motion of gas molecules, there will be a decrease in static pressure in relation to kinetic pressure. Gas molecules along the sides of the trachea, in comparison to those in the center, increase their velocity and kinetic pressure when passing around the vocal folds due to traveling a greater distance. The gas molecules moving along the surface of the vocal folds have a reduction in static pressure. Vocal folds, being pliable and movable, will move toward the center of the trachea due to this difference in pressure. Airflow ceases when the vocal folds are fully adducted. A momentary build-up of pressure occurs as airflow (or "attempted flow") from the lung continues. Vocal folds are set in motion when the pressure below becomes greater than the pressure above, blowing them open (20). Production of sound is dependent on constant repetition of the activity. Additionally, a change in the frequency at which the vocal folds vibrate is dependent on the length (increasing frequency as length increases), mass (decreasing frequency as mass increases), tension (increasing frequency as tension increases) and speed of airflow over the vocal folds (20). A combination of these factors determines the fundamental frequency of the vocal fold

vibration. Abnormal combinations of tension, mass, and airflow cause or contribute to voice problems.

Human vocal intensity, e.g., level of loudness, has a wide range. Production of different intensities results from variations in the size and shape, secondary to muscular activity, of the vocal tract acting as a resonator of sound, in combination with airflow and pressures (20). Variability of intensity is due to changes in the subglottal air pressure in that increased pressure results in greater intensity. However, the actual controlling mechanism of intensity variation is not the change of subglottal air pressure, but the degree and time of closure of the vocal folds producing a resistance to airflow across the vocal folds (20). Glottal resistance is primary factor of intensity variability at low frequencies, whereas airflow is principal factor at high frequencies. Abnormal production of sound levels, i.e. insufficient intensity, may result from inability to completely close the glottis setting up a vicious cycle of increasing expiratory pressure leading to vocal fold fatigue and poor voice quality. Variation of frequency components in a tone is another factor of intensity. The pitch of the voice, its spectral composition influences loudness, the perceptual correlate of intensity, and environmental factors such as distance from the speaker, room acoustics, diffraction, and interference (20).

Another characteristic of sound production, voice quality, identifies an individual and sets him or her apart from another. Voice quality is influenced acoustically and physiologically. Spectrum, the number and amplitude of the frequencies present in a complex tone influence voice quality. Physiologically the shape and length, cross-sectional area, and ratio of oral to pharyngeal cavity size effect voice quality (20).

Control of speech originates in the CNS and the PNS and damage to these areas results in pathological speech in neurological and neuromuscular disorders. Impairments may occur in perceptual voice signs and symptoms, acoustic signs, physiological signs, laryngoscopic and/or stroboscopic signs (20).

Upper and lower motor neuron level of control of speech has been concisely described by Hartman (66). Within the CNS, the upper motor neuron level, two major divisions influence speech. The first, the pyramidal tract, is chiefly responsible for governing skillful, discrete, and finely graded movements, in speech. The second, the extrapyramidal system, helps regulate movements generated by the pyramidal tract, serving to govern muscle tone, strength, speech, and coordination of movement (66). Within the PNS, the lower motor neuron level, the primary phonatory and resonatory control is regulated by the cranial nerve X and its branches, the superior laryngeal and recurrent laryngeal nerves, both providing sensory and motor input to the glottis and supraglottic structures. Dysfunction in speech due to lower motor involvement result from lesions involving the superior laryngeal (its component branches, the internal and external laryngeal nerves), the recurrent laryngeal, and cranial nerves five, seven and the cervical portions of the twelfth (66).

Disordered phonation and resonance, neurogenic dysphonia, due to damage of the central nervous system or peripheral nervous system co-occur with alterations in other aspects of motor speech, specifically articulation, respiration, and speech rhythm (prosody) (66). Damage to the upper or lower motor neurons subserving motor speech results in a group of neuromuscular speech disorders, the dysarthrias, which have signs including aberrations of phonation and resonation (66). Principle signs of dysarthria

include weakness, slowness, incoordination, and altered muscle tone, conditions, which variably affect all components of motor speech. Each form of dysarthria has it's own characteristics.

Six differentiated dysarthrias have been defined and described extensively: spastic, hyperkinetic (quick and slow forms), hypokinetic, ataxic, flaccid and mixed (25). *Spastic* (pseudobulbar) dysarthria, due to bilateral damage of the corticobulbar tracts, is characterized by weak, hypertonic musculature, hyperactive reflexes, harsh strain-strangled ("wail-like") voice quality with reduction in pitch and loudness, and weak cough (66). *Hypokinetic* dysarthria, resulting from damage to the substantia nigra, striatum and their tracts, is characterized by a monopitched, decreased or monoloudness, short phrases, hurried generation of speech, abrupt interruption of speech, breathy and hoarse voice (66, 126). Hypokinetic dysarthria of Parkinson's disease is more often due to chest wall rigidity then abnormalities of the respiratory muscle pump or the gas exchange mechanism (126). The quick form of *hyperkinetic* dysarthria is due to lesions of the striatum and globus pallidus. It is characterized by involuntary pitch and loudness changes, voice arrests due to laryngospasms (spastic dysphonia), harshness and strain-strangled quality, variable breathiness, and intermittent hypernasality in (66). The slow form *hyperkinetic* dysarthria has similar characteristics as the quick form plus the presence of prolongation of the neutral vowel (66). Additionally, the slow form of hyperkinetic dysarthria is not characterized by hypernasality. *Ataxic* (cerebellar) dysarthria, due to bilateral diffuse damage to the cerebellum or possibly unilateral lesions of the left cerebellar hemisphere, is characterized by monopitch being frequently low, to irregular variations in pitch, harsh voice quality, and coarse changes in volume subse-

quent to asynchrony of respiration and vocal fold movement (66). *Flaccid* dysarthria, due to damage of the lower motor neurons of speech, is characterized by weakness, hypotonicity, atrophy, fasciculations, hypernasality, nasal emission and hypoactive reflexes, i.e. reduced gag reflex and cough reflex (66). The primary phonatory sign is hoarseness with a wet, fluttering quality (66). The amount of impairment depends upon the number and extent of cranial nerves, spinal nerves, or muscles involved (66). *Mixed* dysarthria, due to lesions involving multiple sites within the CNS and/or the PNS, results in varying degrees of dysarthria. Involvement of upper and lower motor neurons, as in amyotrophic lateral sclerosis (ALS) (31, 67, 80, 144) is characterized by signs and symptoms typically seen in spastic and flaccid dysarthrias (31, 66, 80, 144) e.g., imprecise articulation of consonant and vowels, hypernasality, harshness, a strain-strangled vocal quality, voice tremor, and slow speaking rate (31, 142). Mixed dysarthria in PwMS, due to the diffuse demyelination of white matter throughout the cerebrum, brainstem, cerebellum, and spinal cord, is characterized by harshness, breathiness, impaired pitch control, variable hypernasality and nasal emission, and reduced respiratory support for speech (66).

Components of speech may be used as an assessment of respiratory function. Reduction in phonation time may be used to predict VC. A phonation time of less than 10 seconds has been associated with a VC of less than one liter, while a phonation time of greater than 10 secs has been related with a VC of greater than one liter (67). Components of speech, assessed by examining aerodynamic (phonatory airflow, cycle-to-cycle variation of phonatory airflow and coefficient of variation for phonatory airflow) parameters and acoustic (fundamental frequency, jitter, shimmer, coefficient of variation

for intensity, and number of harmonics in the frequency spectral analysis) parameters, have been used to assess the presence or absence and the progression of bulbar involvement in patients with mixed dysarthria (80, 142, 144). Assessment of these parameters identified neural involvement prior to clinical signs in patients with mixed dysarthria of ALS (80, 142, 144). Acoustic measures of phonatory function have been used to assess speech intelligibility, which is progressively impaired in mixed dysarthria (80). Early identification of dysfunction in the neural activity may permit more effective intervention and increased retention of vocalization skills for a longer time period. Periodic clinical evaluation may also be used to document the progression of the neural pathology. Specific speech pathology seen in the mixed dysarthria typical of PwMS will be discussed below.

Detraining

Detraining is the partial or complete loss of training-induced adaptations, in response to an insufficient training stimulus. Short-term detraining is defined as being less than four weeks while long term detraining is greater than four weeks (122-124). Following a short-term detraining marked alterations were found in the cardiorespiratory system, including decline in VO_2max, decreased stroke volume, increased heart rate, reduced maximal cardiac output, cardiac dimensions, and ventilatory efficiency. Metabolic changes included increased reliance on carbohydrate metabolism during exercise, reductions in insulin sensitivity and GLUT-4 transporter protein content coupled with a lowered muscle lipoprotein lipase activity, resting muscle glycogen returned toward baseline levels, and reduced concentration lactate threshold (122, 123). Detraining changes at the muscle level include reduced capillary density and oxidative

enzyme activities, and reversal of training-induced changes in fiber cross-sectional area, but strength performance declines are limited (123). Häkkinen et al, (58) reported a decrease in isometric strength following 3 weeks of detraining after a 24 week training protocol. However, following 24 weeks of detraining decreases were found in the muscle cross sectional area, the one repetition maximum, the isometric force, and a return toward baseline of maximal voluntary neural activation of the agonists with increased antagonist co-activation, in the presence of minimal reduction in explosive jumping and walking (58). Häkkinen and colleagues (57), using a 6 month strength training protocol, reported a significant loss of strength in their patient population following a prolonged detraining period of 3 years. Investigators, examining exercise capacity of patients who had received either a single or double lung transplant, reported that the reduced exercise capacity due to diminished leg power and work capacity in the presence of maintained respiratory muscle strength was due to detraining (91).

Muscle quality, the muscle force production per unit of muscle mass, has been used to describe the relative contributions of non-muscle mass components to changes in strength following strength training. Muscle quality increased following 9 weeks of strength training and remained elevated above baseline following 31 weeks of detraining suggesting that factors other than muscle mass, i.e., neuromuscular factors including increases in motor unit recruitment, decreased coactivation of the antagonist muscle, contribute to strength gains (75).

Detraining of the respiratory muscles has been very limited. A recent investigation examined inspiratory muscle training in healthy subjects who trained for 9 weeks followed by either 18 weeks of detraining or maintenance. The subjects who

participated in the detraining had a loss of inspiratory muscle function at 9 weeks which plateaued between 9 and 18 weeks but remained above pre-IMT values (147). Baker (5), examining, EMST in healthy subjects, reported that those who trained for 4 and 8 weeks had similar loss of expiratory muscle strength (i.e., 9%) at the fourth and eighth week of detraining. However, the investigator reported that expiratory muscle strength remained above baseline (5). Gosselink et al (52), examining respiratory muscle strength training in PwMS reported that an increase in inspiratory muscle strength, which decreased following the cessation of training, remained above baseline at the end of a 3 month detraining period.

Multiple Sclerosis

MS is one of the more prevalent neuromuscular diseases with the incidence in the USA and Canada currently between 350,000 to 550,000 people (4). The incidence of MS varies considerably in different parts of the world. The low risk zones (in the United States, the southern half of the country) have a prevalence rate of less than 20 per 100,000 population, while the high-risk zones (in the United States, the northern half of the country) have a prevalence rate higher than 40 per 100,000 (26).

MS, also known as disseminated sclerosis (113, 114, 136) (136), is a neurogenic disease whose principle signs and symptoms are due to demyelination of CNS tissue, particularly the motor pathways (38, 176). Lesions are widely present throughout the CNS particularly in the periventricular areas (38, 176). Clinical signs and symptoms of MS result from dysfunction within the CNS and rare PNS involvement (160, 163, 164, 184). Decreased respiratory muscle strength and endurance, in both the inspiratory and

the expiratory muscles with the greatest weakness occurring in the expiratory muscles, result in reduced respiratory volumes, which may complicate MS. Reduced respiratory muscle strength and endurance may give rise to symptoms such as reduced exercise capacity, impaired speech, and impaired cough, which may precipitate atelectasis and pneumonia, leading to acute respiratory failure (38, 51, 130, 171). Incidence of death due to bulbar dysfunction ranges from a low of 1% to 2% to nearly 50% (12, 51). Occurrence and presentation of respiratory symptoms are variable and may depend on nationality, as higher occurrence of respiratory dysfunction seems to exist in Japanese and Filipino MS patients compared to Western MS patients (192).

Respiratory Dysfunction in Persons with MS

Respiratory complaints are rare, but respiratory dysfunction is common in patients with MS, causing controversy as to the occurrence of respiratory involvement. Respiratory muscle strength may be reduced in patients with mild disease (15, 51, 170). Respiratory involvement occurring early in the course of the disease is mostly due to reversible neuromuscular failure (15). Respiratory compromise, including acute respiratory failure, previously considered a condition rarely associated with MS (3, 15), has been found to be common in MS particularly during the terminal stage (6, 15, 51, 171). Acute respiratory failure may be rare, but occurs in patients with moderate to severe respiratory muscle weakness and in patients challenged by relatively minor added respiratory loads, e.g. as associated with an otherwise uneventful respiratory infection (3, 51, 182). The actual prevalence of respiratory problems in PwMS is not known, however due to the incidence of MS in the US, a significant number of individuals may be at risk.

Respiratory muscle weakness in individuals with MS is very similar to that seen in other neuromuscular or neurological disorder (6, 48, 51, 54, 87, 93, 176, 182). Neural dysfunction may result from abnormal control of breathing, conduction block, as well as involvement of the descending respiratory pathways, lower respiratory neurons, and anterior roots (90). Respiratory muscle weakness has been associated with significant bulbar or diaphragmatic and/or limb paralysis (12, 21, 56, 61, 128, 143). Unilateral or bilateral diaphragmatic paralysis may present as apnea during awake and/or sleeping hours (51, 73, 143). Dyspnea and Cheyne-Stokes respiration occurs early or late in the disease (56). Dyspnea, the sensation of difficult breathing, may be related to the sensation of increased muscle tension conveyed by afferent mechanoreceptors and corollary discharge. Though severe respiratory muscle weakness may occur in MS, patients rarely complain of dyspnea (90). Demyelination delays transmission of the neural impulses to the inspiratory and expiratory muscles before demonstrable muscle dysfunction (90). Severe muscle dysfunction may be accompanied by little or no lung volume loss (15). However, by the time shortness of breath (SOB) becomes noticeable, performance during pulmonary function tests shows a restrictive pattern with reductions in VC, FEV_1, and peak expiratory flow rate, as well as increases in RV, RV/TLC%, thoracic lung volume, airway resistance and specific airway conductance (3, 15, 87, 171). Performance on pulmonary function tests is related to muscular strength measured as mouth pressure.

Greater numbers of patients with MS exhibit abnormal maximal expiratory pressure (MEP) than maximal inspiratory pressure (MIP), however both MEP and MIP are markedly reduced (15, 51, 177). Greater reductions in MEP may be due to slow

ascending paralysis in MS starting from the lower extremities. Respiratory muscle weakness has been associated with fatigue a common and often disabling feature in patients with MS (56). Muscle (physiological) fatigue is the failure to maintain a determined force output, which is recoverable by rest. Fatigue of MS from a patient's viewpoint, is defined as a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities (22). Fatigue of MS is associated with reduced tolerance for any and all physical activities including ADLs and exercise (43). Reduced exercise tolerance due to the neurological dysfunction of the motoneurons to the skeletal muscles is associated with RMW and/or fatigue (51, 176). Fatigue of MS may be due to impairment of the respiratory muscles and/or the skeletal muscles. MS as it relates to fatigue may be associated with abnormal peripheral exercise response, namely, problems in peripheral oxygen utilization (41). Dyspnea experienced during exercise and at rest in individuals with MS occurs because of skeletal muscle dysfunction and respiratory muscle weakness and/or fatigue (38, 176). However, no studies have attempted to link subjective fatigue with respiratory muscle weakness in PwMS (22).

Laryngeal muscle weakness, due to plaque formation or demyelination in the brainstem may lead to dysphagia, which is dysfunctional swallowing (136, 146). If expiratory muscle weakness is present along with bulbar muscle weakness spontaneous coughing to prevent aspiration may be impaired (136, 146). Rogers and associates, (146) reported the case of an individual with MS in whom a gag reflex could not be elicited during intake of liquid and /or food. Spontaneous cough was present, however, the patient's oxygen saturation which was initially 97% at rest dropped to 87% during liquid

intake and 80% during food intake (146). Inefficient cough precipitates greater desaturation and higher risk of aspiration. Inefficient cough may be present in PwMS who have brainstem and/or cervical involvement having mild to severe levels of disability (105, 146).

Cough Impairment in Persons with MS

Cervical spinal cord involvement in PwMS results in similar injuries as patients with transection of the cervical spinal cord, with expiratory muscle weakness associated with inadequate cough due to reduced expiratory flow rate (46). Expiratory function and muscle strength correlate with neurological level (46). Reduced air flow impairs ability to clear pulmonary secretions, which predisposes an individual to respiratory infections (73, 171, 176). As in other neurological disorders, such as stroke, lesions in the brainstem result in a much higher incidence of impaired laryngeal cough reflex (1). Likelihood of aspiration and aspiration pneumonia is higher in individuals with reduced bulbar function due to expiratory muscle dysfunction (2, 93, 160, 176).

Coughing may occur in the presence of normal functioning vocal folds and cardiopulmonary function. It has been suggested that coughing, as a tussive crisis, constitutes a paroxysmal symptom in multiple sclerosis (76). Impaired cough, due to weakness of the abdominal muscles, was improved through magnetic stimulation of the expiratory muscle activation (102). Strength of cough measured subjectively and "objectively" by the Index of Pulmonary Dysfunction (IPD), was significantly improved after 3 months of training compared with the control group ($p<0.05$). After 6 months, the IPD remained significantly better in the training group (52). The IPD has limitations as it was found to be able to identify all subjects with normal expiratory muscle strength

(PEmax greater than or equal to 80% of predicted); however, not all patients with isolated expiratory muscle weakness were correctly identified (166).

It is not known if voluntary activation of the abdominal muscles through the use of an expiratory muscle trainer will increase muscle strength sufficiently to improve cough in individuals with MS. No study exists, at this time that has objectively examined the relationship between expiratory muscle strength and cough in patients with MS.

Speech Impairment in Persons with MS

Pathophysiological signs, such as increasing incoordination, spasticity and weakness of the muscles in the body, may occur in speech and vocalization when the laryngeal muscles are involved. Speech impairment may be of gradual or rapid onset, progressive or non-progressive, or occur as a paroxysmal sign or symptom (32, 50, 53, 106, 121, 127, 195). Speech and vocal impairment may present as: 1) impaired phonatory coordination and control and by reduced range and force of articulature movement; 2) spasticity and muscle weakness affecting the ability of the vocal folds to adduct smoothly and to maintain the proper adductory forces needed for phonation; 3) inability to produce the proper subglottal pressures needed for speech secondary to weakness of vocal fold adduction, manifested as reduced vocal loudness; 4) spasticity which may impair the ability to maintain control over vocal fold adduction causing uneven vocal loudness; 5) aperiodicity of the vocal fold vibration, leading to greater perceived hoarseness/harshness due to poor coordination of the vocal folds; and 6) impaired rate of movement of the vocal folds (61, 64, 185).

Speech and voice impairment, reported to occur mostly late in the disease process of MS, are considered not pervasive in PwMS (26). Dysarthria and scanning speech,

once considered a cardinal sign of MS (20) have been considered pathognomonic for MS. However, early investigators reported speech impairment as a limited occurrence in MS. Osterman and Westerberg (132) reported that less than 3% of 235 individuals with undoubted or suspected MS had paroxysmal dysarthria. Darley et al, (26) reported normal speech, minimal impairment and moderate to severe impairment in 59%, 29%, and 12% respectively, of their 168 patients. Of their 168 patients 28.8% reported that they used communication augmentation equipment. Beukelman and associates (8) noted 23% of the total sample of 656 people reported the presence of "speech or other communication problems." Four percent of the total sample indicated that strangers were unable to understand them (8). Kurtzke et al, (86) reported that scanning speech was present in only 18.9% of their 525 male patients with MS (20). Dysarthria in PwMS has occurred with the loss of voluntary respiration due to bilateral involvement of the corticospinal tracts, in the presence of continued automatic (spontaneous) breathing (128).

In contrast, other investigators have noted higher incidences of impairment. Some have reported dysarthria in approximately 40% of patients with MS (115). A survey of patients with Parkinson's disease (n=200) or MS (n=200) showed that speech and swallowing difficulties are very frequent within these groups (65). Forty-four percent of the MS patients had experienced impairment of speech and voice after the onset of their disease. Speech disorder was regarded as one of their greatest problems by 16% of the MS patients. Only a very small number of patients, 2% of the MS group (n =4), had received any speech therapy (65). In a recent study, 51% of 77 individuals with

MS displayed mild to severe dysarthria, which occurred in all components of speech production: respiration, phonation, prosody, articulation and nasality (63).

The dysarthria of MS is a mixed (having ataxic and spastic dysarthria characteristics) dysarthria with disorders of voice intensity, voice quality, articulation, and intonation (115). Investigators noted "...when a predominant type of dysarthria existed, it was not generally associated with a characteristic profile of neurological deficits. Rather, severity of speech deviation was positively correlated to overall severity of neurological involvement, type of disease course, and number of years in progression" (63). Principle speech impairments found in PwMS include impaired loudness, harshness, defective articulation, impaired emphasis, impaired pitch control, hypernasality, inappropriate pitch level and breathiness (20, 26). Vocal fold impairment, reduced range of motion of the vocal folds and momentary stoppages of vocal fold motion, may occur secondary to abductor paralysis, which causes low flows and difficulty in generating high subglottal pressure problems (20). Severity of vocal impairment increases with progression of the neurological pathology.

Speech requires the use of the respiratory system mechanically, that is, for the generation and control of the airflow and pressures needed for speaking (20). Formerly, scanning speech was considered a primary dysfunction, that is a component of the characteristic triad of signs in MS along with nystagmus and intention tremor (26). Mixed dysarthria is considered pathopneumonic for MS (126). Impaired loudness of voice may be present with scanning speech and/or vocal tremor making understandable communication impossible (8, 26, 61). Impaired loudness control occurred in over half (77%, that is 130 out 168) of a series of PwMS examined for significant speech

deviations (26). Decreased VC was associated with poorer control of loudness, more trouble prolonging a vowel, and increased breathiness (26). PwMS with voice symptoms often present with hoarseness / harshness (20). Medical attention is sought in approximately 50% of the patients initially due to ear, nose and throat symptoms, including vertigo, nystagmus, dysarthria or dysphagia (20). Unilateral or bilateral abductor paralysis of the vocal folds may occur (20). As yet, there has been no investigation as to the effect expiratory muscle training in PwMS might have on improving dysfunctional communication.

Detraining In MS

As previously describe there has been only one study examining detraining in individuals with MS. Gosselink et al, (52) reported a reduction in strength which remained above baseline level following 3 months of detraining.

Previous Respiratory Muscle Training Studies

A limited number of studies, five to date, are available that have examined respiratory muscle training by itself or as a component in an overall exercise program in PwMS. The studies are presented in chronological order from the earliest to the latest. Olgiati and associates were the first to use respiratory muscle training in PwMS (131). The investigators stated that all patients were in a stable phase of their disease. Level of disability was not given. Eight patients trained twice daily, breathing against an external resistance 3 to 5 minutes for two sets, for 4 ± 1 weeks. Training employed a resistive method performed more in an endurance manner. The type of resistance (inspiratory and/or expiratory) was chosen depending on whether PImax or PEmax was reduced to <70% of predicted. Training produced a 31% improvement in both PImax and PEmax

and a 21% gain in MVV. Limited number of subjects, training time, and description of training method makes comparison to the other studies difficult.

Smeltzer and co-workers (168) compared the effects of expiratory muscle training and sham training on respiratory muscle strength. Ten subjects completed 3 months of expiratory muscle training using a pressure-threshold load training device. Five subjects completed 3 months of sham training using the same device, but without an expiratory training load. Participants had a high level of disability as the patients' EDSS score ranged from 6.5 to 9.5 indicating wheelchair bound to bedridden (85). Daily training consisted of two periods separated by at least 4 hours with each training session made up of 3 sets of 15 repetitions loaded expiratory breaths. MIP and MEP were assessed at baseline, and after 1, 2, and 3 months of training. Actual level of load was not reported nor was the schedule of increasing resistance. Baseline assessment of MEP (mean = 56.8 ± 16.4 cm H_2O; 36.9 ±14.6%) and MIP (mean = 46 ± 16.7 cm H_2O; 45 ± 17.1%) indicates weakness. Increase in expiratory muscle strength, assessed after 3 months of training, ranged from 2.8 to 35.9 cmH_2O). Five (50%) of the participants in the experimental group had an increase in MEP greater than 20 cm H_2O (168). Overall improvement was reported as a 34% from baseline to post-training. The investigators reported anecdotal responses of the participants which included: 1) through participation in the training program they had become more aware of their breathing and consequently deliberately took deep breaths periodically; 2) their respirations had been shallow and as a result of the training (or their participation in the study) their respirations had become deeper; 3) they were able to lie flat in bed without becoming as short of breath as

previously; and 4) their voices were described by others unaware of their participation in the study as stronger and louder than before training (168).

Wiens and associates (189) reported the outcome of a pilot study investigating respiratory muscle training through the use of music therapy, which emphasized diaphragmatic breathing and coordination of breath and speech. The experimental group consisted of nine participants and the control group consisted of 10 participants all with advanced MS (EDSS scores ranged from 7 to 9; the mean score was 8.3. These subjects were restricted to wheelchairs, the major of who used electric wheelchairs. Per the investigators description "the experimental group received three individualized 30-minute music therapy sessions per week for 12 weeks. … of three major components: relaxation and diaphragmatic breathing, intonation of syllables, and reading or singing phrases, paragraphs, and simple songs. Diaphragmatic breathing exercises, which challenged the volume of breath intake and the rhythm of breathing" (189). Respiratory muscle strength, evaluated as MIP and MEP, was assessed at 6 and 2 weeks before and 2 and 6 weeks after intervention. An increase of 10 cmH_2O values from pre- to post-test was considered to be a clinically significant improvement. Within the experimental group 5 of 9 subjects improved MIP, ranging from 1.5 cm H_2O to greater than 20 cm H_2O, while 6 of subjects improved MEP, ranging from less than 5 cm H_2O to greater than 15 cm H_2O. Improvement occurred between two weeks prior to and two weeks post initiation of the intervention. Investigators reported that within the control group three participants improved by 10 cm H_2O or more in terms MIP and one participant improved by 5.5 cm H_2O in terms of MEP. Improvement, though clinically significant, showed no statistical

improvement in expiratory muscle strength compared to the control group following 12 weeks of individualized music therapy (189).

Gosselink and co-workers (52) examined both the contribution of respiratory muscle weakness to patients' impaired health status and the effect of expiratory muscle strength training to FVC, cough efficacy, and functional status in PwMS. The second part of the investigation examined the effect of expiratory muscle strengthen training. Investigators adapted the Threshold®, a device for expiratory loading. Eighteen bedridden or wheelchair-bound MS patients (EDSS ranging from 7 to 9.5) were separated into two groups of nine participants for an experimental and a control, respectively. Training participants completed 3 series of 15 contractions against an expiratory resistance of 60% PEmax two times a day, whereas the control group performed breathing exercises to enhance maximal inspirations (52). Expiratory training enhanced both inspiratory and expiratory muscle strength. Following three months of training the PImax was statistically improved over baseline but not greater than the control group. PEmax changes were higher in the training group compared to the control, but did not reach statistical significance. Patients with MS are able to improve their respiratory muscle strength; sufficiently that at six months post training the IPD remained significantly better in the training group compared to the control group.

Klefbeck and Nedjad (83) examined whether inspiratory muscle training improves inspiratory muscle strength, respiratory capacity, fatigue, and subjective perception of physical endurance in PwMS having advance disease. Subjects (7 trained and 8 controls) using a Threshold inspiratory trainer, completed three sets of 10 repetitions at 40 % to 60 % of their PImax, twice every other day over a 10-week period.

Though the subjects trained the inspiratory muscles there was a 36% improvement in the expiratory muscle strength. Training had no affect on respiratory parameters, such as FVC, FEV_1, FEV_1/FVC or PEF. Training did not improve the subjects' subjective perception of physical endurance after bathing and dressing in the morning. No correlation was found between EDSS and FSS scores.

Summary

Why is another study of respiratory muscle strength training in individuals with MS needed? Two of the previous studies have used more of an endurance method of training instead of a strength training modality. It is muscle weakness not endurance that results in diminished respiratory cough and speech. The previous studies had subjects who had high level of disability, per the EDSS. It is now known that the higher level of disability is not due to just demyelination but to axonal damage – damage that is not repairable. In choosing subjects earlier in the disease respiratory muscle weakness has a greater chance to positively respond to the training due to the presence of less irreversible neurological damage. Previous studies have not related the change in respiratory muscle strength to functional outcomes or quality of life issues. Strength in and of itself is important, but if increased strength can improve function or quality of life issues than the training will be of greater benefit. Finally, no previous study has examined respiratory strength training and improvement in speech in persons with MS.

CHAPTER 3
PROCEDURES

All participants in this project signed an informed consent document authorized by the Institutional Review Board of the University of Florida.

Recruitment of Participants: Individuals were recruited through printed fliers, announcements at various MS support group and educational functions, and personal contacts. No monetary compensation was given to the participants. Individuals who wished to retain their training device following study completion were permitted to do so.

Subjects

Fourteen healthy individuals [2 males, mean age = 43.4, range 29 to 56 and seventeen individuals with MS [3 males, mean age = 48.7, range 32 to 58] were recruited. The healthy individuals served as a control group and were age and gendered match to the PwMS. All subjects received expiratory muscle strength training (EMST). Any PwMS who met the inclusion and exclusion criteria was accepted into the project. Each participant with MS was assessed as to level of disability per the Extended Disability Status Scale (EDSS, see Appendix A) (21). The EDSS provides a score ranging from zero, indicating normal neurological findings, to 10, indicating death from MS. The EDSS score is determined from the Functional Systems Scale (FSS, see Appendix A-2) which scores function in the pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual and cerebral systems on a scale of 0 being normal to 5 or 6; the higher the score the more dysfunctional the system. The EDSS gives a comprehensive measure of the disability, while the FS allows extremely different symptoms to be

evaluated on the basis of the involvement of the main neurological functions. Participants had mild (1.0 to 3.0, with one or two FSS grade 2, with others 0 or 1) to moderate disability (3. 5 to 6.5, ambulatory with or without assistive devices for a distance of 20 feet without a rest; usual FSS equivalents with combinations of more than two FS grade 3+).

During the study one healthy subject dropped out due to conflict with work and five individuals with MS were not included: one got a new job and could not make the assessments and training sessions due to her new work schedule; two individuals indicated they were seeing their doctor later in the week due to new symptom suggestive of an exacerbation; and one individual had an EDSS score above that acceptable for the study.

Inclusion criteria

For all subjects:1) no known cardiac, pulmonary (e.g., Asthma, COPD, pulmonary fibrosis), neurological (other than MS), or orthopedic conditions that adversely effect the respiratory muscle pump or gas exchange system; 2) in their third to sixth decade of life (i.e. 20 to 59 yrs of age), 3) adequate vision to read the speech passages, and 4) native English speaking.

For PwMS:1) a definite diagnosis of MS (100), 2) mild to moderate disability as assessed by the EDSS, 3) no exacerbation in the prior 3 months, 4) ability to follow spoken and written instructions, and 5) sufficient facial muscle strength to achieve and maintain lip closure around a circular mouthpiece.

Exclusion criteria

For all participants: 1) known cardiac, pulmonary, neurological (other than MS) or orthopedic conditions that adversely effect the respiratory muscle pump, 2) current smoker or had smoked within the last five years, 3) prior participation in a respiratory strengthening program either for research or therapy.

Data Collection

Participants were seen at three assessment sessions, (pretraining, post training, and detraining) and once per week during the training phase of the protocol. The pretraining assessment occurred within 24 hours for 50% of the subjects starting training. For the other subjects, time between pretraining testing and beginning of training ranged from 3 days to 6 days, as it was the design of the project to have subjects train Monday through Friday. The post-training assessment occurred within 24 to 48 hours of the completion of training. Fifteen of the 17 individuals with MS were seen on two separate days for data collection at each of the three assessment sessions. This was done to minimize the possibility of fatigue. Two of the seventeen wished to have the assessment completed all at one time due to work commitments. The assessment of each of the healthy controls was completed on one day for that subject.

Description of Procedures

Laryngeal Endoscopic Examination (MS participants only)

Individuals with MS were seen at the pretraining and post-training assessments for an evaluation of their vocal folds by endoscopic examination. Fifteen of the seventeen received a rigid laryngeal endoscopic examination. The endoscopic examination was performed by a board certified Ear, Nose and Throat (ENT) physician

or licensed speech pathologist with extensive experience in performing endoscopic examinations. The subject sat in the endoscopic examination chair and leaned forward. The endoscope used was either a rigid or a flexible scope connected in series to an endoscopic unit (RLS 9100B, Rhino Laryngeal Stroboscope Kay, Elemetric Corp NJ, USA). Use of the flexible or rigid scopes was dependent on the level of gag-reflex of each participant. During rigid endoscopic examination the examiner held the subject's tongue with a 4 x 4 gauze while moving the endoscope towards the back of the oral cavity. For those subjects with whom the flexible scope was used, the participant first received a nasal dilator (Afrin), which was followed by application of a topical anaesthetic (lidocaine) both of which were administered through one of the nostrils into the nasal passage. A gel lidocaine was applied to the sides of the flexible prior to placing it in the nose. The scope was then progressed through the nasal passage to the top of the interior of the nose with tip the endoscopic camera projecting down the nasal pharynx. Tasks included: 1) the subject saying the vowel /i/ in its long form i.e., 'ee', 2) the subject performing vowel slide, e.g. going from a high pitch to a low pitch and back up, and 3) taking a normal or deep breath. Each task was completed 2 to 3 times while being viewed and recorded under halogen light and under strobe light. Recordings were placed on a master tape and viewed in randomized order without participant identifiers being available to the examiners. The vocal folds were examined as to appearance and movement. Examination of the recorded endoscopic examinations were completed by the board certified ENT physician who had performed about 50% of the examinations and the speech pathologists who had performed the remaining examinations.

Assessment Procedures (All Participants)

All participants were seen at pretraining, post-training, and detraining assessment sessions for all tasks described below. Sequence of the procedures was randomized. Instructions to the subjects for each procedure were standardized, (i.e., for cough – take two normal breaths and on the third one take in as much as you can, filling your lungs completely, then cough it out)

Maximal Respiratory Pressures

Maximal expiratory pressure (MEP) and maximal inspiratory pressure (MIP) were assessed using a hand held digital manometer (Micro Mouth Pressure Meter, MP01, Micro Direct Inc., Auburn ME). The maneuver was performed by the subject as he / she placed his / her mouth around a disposable mouthpiece, with his/her nose closed by a noseclip. Each maneuver was performed while standing unless prohibited by the subject's balance. For MEP the subject inhaled fully, placed his / her mouth around a disposable mouthpiece then blew the air out as hard and fast as possible. Instructions to the participants were: 1) take in as much air as you can, 2) blast it out, and 3) go, go, go… For MIP the subject exhaled fully, placed his / her mouth around a disposable mouthpiece then inhaled as hard and fast as possible. Instructions to the participants were: blow all the air out of your lungs, until you can not get any more out; suck it in hard and fast. Subjects were verbally encouraged by the repeating of "go, go, go. " The maneuver was performed 3 to a maximum of 10 times. Previous investigators have recommended that as many as 10 times are needed to achieve proficiency in performing maximal maneuvers. The top three measurements were averaged for the data analysis.

Pulmonary function tests

Pulmonary function tests (PFTs) were completed on a MasterScreen PFT (Jaeger Toennies, Erich Jaeger Gmbh, Leibnizstrasse 7,D-97204 Hoechberg). During the performance of the PFTs the subjects sat while they used the MasterScreen PFT (per manufacture recommendations). Due to diminished balance 2 PwMS sat during all testing. The guidelines of the American Thorax Society were followed. Briefly, subjects 1) placed his / her mouth around a disposable mouthpiece, with his/her nose closed by a noseclip, 2) took two normal breaths, 3) exhaled fully and with as much force as possible, being encouraged to blast out all the air in the lungs, and 4) to inhale fully and with as much force as possible. Participants received the following instructions: 1) take a normal breath, a second normal breath, 2) now take in as much air as you can, 3) blast it out hard and fast, 4) keep going, and 5) suck it back in. Subjects were verbally encouraged while performing the maneuver. Respiratory parameters included forced vital capacity (FVC), forced expiration in the first sec (FEV_1), ratio of FEV_1 / FVC, peak expiratory flow (PEF), mid forced expiratory flow (FEF_{25-75}), inspiratory vital capacity (VC IN). The unit provided predicted, actual, and percent of predicted. The maneuver was completed three times and the best of the actual measurement was used for analysis.

Airway resistance

Airway resistance was assessed using an Impulse Oscillometer System (IOS), a self-contained computerized system for performing impulse oscillometry measurements (MasterScreen IOS, Jaeger Toennies, Erich Jaeger Gmbh, Leibnizstrasse 7,D-97204 Hoechberg). The IOS uses random pulses of 5-35 Hz generated via a small loudspeaker mounted in parallel to a mouthpiece connected to a pneumotachometer. Pressure-flow

oscillations are superimposed on the subject's breathing pattern. Real-time recordings of mouth pressure and flow are used to estimate total respiratory system, impedance (Zrs) and its two components, resistance (Rrs) and reactance (Xrs). The subject, seated, placed his / her mouth around a disposable mouthpiece with his/ her hands on his/ her cheeks to prevent loss of the measuring signal. The subject breathed normally for a minimum of 30 sec to establish a consistent breathing pattern prior to data recording, which took 30 to 45 sec or stopped automatically at a maximum of 90 sec. The maneuver was repeated three times. Data of interest were tidal volume (VT [l]), total airway resistance at 5 Hz (R5Hz [$cmH_2O/(l/s)$]), central airway resistance at 20Hz (R20Hz [$cmH_2O/(l/s)$]), reactance (X5Hz [$cmH_2O/(l/s)$]), and resonance frequency (Fres, [l/s]), and model parameters for central airway resistance (Rz, [$cmH_2O/(l/s)$]), and peripheral airway resistance (Rp, [$cmH_2O/(l/s)$]). An average of the three trials was used for analysis of the data.

Maximal voluntary cough

Maximal voluntary cough (MVC) was measured using a disposable mouthpiece connected to a Hans Rudolph 800 pneumotachometer (flow head) with a 33.02 cm flexible hose with internal diameter (ID) of 3.5cm. The pneumotachometer was connected to a spirometer (Spirometer, ML140, PowerLab ADInstrument, Grand Junction CO) by two flexible hoses 36 inches long, with internal diameter of .25 inch. The spirometer was connected in series to a recording unit (model 4/20, PowerLab ADInstrument, Grand Junction CO). The recording unit was connected in series to a Macintosh iBook computer. The software program, Chart, version 4.0 for MacIntosh (ADInstrument, Grand Junction CO), was used to collect cough data online and analysis the data off-line. The subject placed his / her mouth around a disposable mouthpiece,

with his/her nose closed by a noseclip, took two normal breaths and then inhaling fully followed by a maximal cough. Subjects were verbally encouraged while performing the maneuver. Subjects completed a minimum of ten coughs. Coughs were rejected for analysis if it was performed more like a PFT maneuver, or if there was significant amount of electrical noise. Therefore subjects may have performed more than the minimum 10 to achieve adequate number of acceptable coughs.

The signal was low-pass filtered at 225 Hz through the filter in the Powerlab unit, as the filter in the spirometer capable of filtering to 100 Hz, was inadequate to filter the high frequency components of the waveform during cough. Data of interest for the cough was flow (L/s), volume (L), peak amplitude (L/s), rise time (ms) [the time taken for the waveform to cross from Lower to Upper threshold limits], and leading slope ($L/sec \bullet ms^{-1}$) [the slope of a line that connects the lower and upper threshold points on the waveform, and a measure of the ratio: peak amplitude/ rise time]. Figure 1 presents a cough wave form with data of interest indicated. An additional variable of interest is the cough volume acceleration (CVA) which is derived from the ratio of the cough peak flow over the time to peak (39). Variable means were analyzed.

Index of Pulmonary Dysfunction (IPD)

Pulmonary dysfunction was assessed through use of the Index of Pulmonary Dysfunction (IPD) in Multiple Sclerosis (Appendix B) (166, 169). The IPD is a clinical assessment of the status of pulmonary function in individuals with MS. It is composed of 4 items: 1) the patient's report of a weak cough and difficulty caring pulmonary secretions, 2) their report as to the strength of their cough, normal or weak, 3) assessment of the strength of their cough by the examiner, and 4) the length of time one is able to

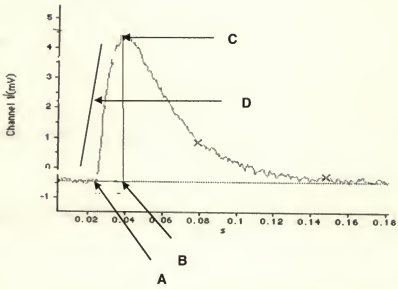

Figure 1. Compression and Exhalation (explosive) phases of cough wave form. Point A is the end of compression phase. Point B is the time to reach the peak value, i.e. the rise time. Point C is the peak value (peak amplitude). Point D is directed toward the tangent along the rise to the peak value, this is the leading slope. Cough volume acceleration is the peak value over the rise time (value of point C/value of point B)

count out loud after a maximal inhalation (167). Score ranges from 4 to 11, with 4 being normal and with more dysfunction the higher the number (166, 169). Score determined at each assessment was entered into the data analysis.

Speech

Acoustic components. The subject was positioned in front of a digital to analog tape (DAT) recorder (model: DTC -ZA5ES, Super Bit Mapping, Sony Corporation of America, New York, NY) connected in series to a microphone preamplifier (model 760x, dbx Professional Products, Sandy UT, USA). Subjects wore a headset microphone (model: SHURE) placed 1 inch from the corner of the subject's mouth. Speech tasks, performed three times at two levels of loudness, normal (N) and loud (L), being twice as loud as the normal loudness, included:1) prolonging the vowel /a/ in its short form 'ah'

and 2) reading the 'Grandfather Passage' (Appendix C) (24). Order of the tasks was randomized, achieved through a shuffling of cards identifying the task to be done. The recording was analyzed by playing the raw signal through a digital to analog tape recorder (TAS CAM DA 302, TEAC America, Montebello, CA) connected in series to a Gateway computer. The signal was analyzed using the software program, Cool Edit (Syntillium Software Corporation, Phoenix, AZ, USA). Data of interest included: for the vowel prolongation - the total time the vowel was audible and for reading of the "Grandfather Passage" (24) - 1) sentence duration, 2) pause duration, 3) total passage duration, 4) articulation rate, and 5) words per minute. The mean of three trials (i.e., three at N loudness and three at L loudness) of each task was entered into the data analysis.

Aerodynamic components. The signal for pressure was recorded using a pressure transducer (low-frequency Pressure Transducer, model: PT L-1, Glottal Enterprises Syracuse NY, USA) attached to a facemask connected in series to a preamplifier (model MS 100-2A, Glottal Enterprises Syracuse NY, USA) which was in series to a 3000 VETTER Digital PCM Recording Adaptor, (AR Vetter Co, Reversberg, PA, USA). The recording unit was calibrated for pressure at 5 cm H_2O and for flow at .5 L/sec with a pressure and flow calibration unit (model MCU-4, Glottal Enterprises Syracuse NY, USA). As the subject repeated "pa" at N and L loudness levels the gain on the channels for pressure and flow was adjusted so that no more 75 to 90% of the available range of each channel was being used. This was done to prevent 'peak-clipping', i.e., cutting off the top of the pressure measurement. The subject held the facemask, covering the nose and mouth area, securely against the face to prevent air leak.

A polypropylene tube with internal diameter of 3mm, connected to the pressure transducer, was positioned behind the subject's teeth within the oral cavity but not being touch by the tongue. The subject repeated the phrase /pa/ seven times at a normal and loud sound pressure level. The raw data was recorded onto video recording tapes set to record 2 hours of material per tape. Raw data was analyzed by playing the pressure signal through a digital to analog converter (Powerlab 8S, ADInstruments, Grand Junction, CO) in series to a table top computer. The software Chart (ADInstruments, Grand Junction, CO) was used to process the signal. The middle five of seven repeated /pa/ were analyzed. The relative change in pressure, measured in millivolts, between assessments was used in the statistical analysis.

Speech Questionnaires

Dysarthria Scale. The Dysarthria Scale used was the Amyotrophic Lateral Sclerosis Severity Scale(193, 194). It is a 10 point perceptual assessment scale which examines an individual's ability to speak, ranging from 1 – nonvocal – vocalization is effortful, limited in duration, and rarely attempted; may vocalize for crying or pain to 10 – normal speech – patient denies any difficulty speaking, examination demonstrates on abnormality (Appendix D). Subjects' speech was assessed throughout each evaluation for determination of the score, as well as asking if the subject or others had noticed changes in their voice in the two months prior to the initial evaluation, during the eight weeks of training, or the four weeks of detraining. The score determined at each assessment was placed into the data analysis.

Voice Related Quality of Life (VRQOL) (Appendix E, items and scoring) (70, 71). This is a 10-point questionnaire using a 5-point likert scale, i.e., 1 – none, not a

problem at all to 5 – problem is as "bad as it can be". An overall score and two subscale scores, physical and social, result and are presented as percents. The influence of the voice on the quality of life in the two weeks prior to the assessment was rated. The higher the percentage, 100% compared to 75%, indicates less voice impairment in voice–related quality of life issues. The percentage score measured at each assessment was put into the data analysis.

Training and Weekly Assessments

Subjects trained 5 days per week, once under the supervision of the investigator and 4 times at home. Subjects used a Positive Expiratory Pressure (PEP) threshold trainer (Threshold®PEP, Healthscan Products Inc, division of Healthdyne Technologies, NJ, USA). The trainer was modified to provide a threshold pressure range of 15 to 160 cm H_2O. Participants completed 4 sets of 6 repetitions per day. Subjects trained for 8 weeks. Subjects were instructed to breath in and out through the unit, maintaining their exhalation for at least 5 secs and to rest a minimum of 30 sec to a minute between sets. Weekly assessments were used to assess training (i.e., correct use of the training tool), re-assess MEP and adjust the training intensity. Training intensity was controlled at a set percentage of MEP, i.e., 40% the 1^{st} week, 60% the 2^{nd} week and 80% the 3^{rd} through the 8^{th} week. MEP was assessed identical to that during the three primary assessment session, i.e., the subject inhaled fully, placed his/her mouth around a disposable mouthpiece, and then forcefully blew out. Three to seven measurements were taken, with the mean of the top three measurements within 10% of each other used for the adjusted intensity. Subjects completed a training log, which requested information on number of

sets and repetitions, rating of perceived exertion, and date. Training compliance ranged from a 90% to 100%

Detraining

Participants returned their training unit to the investigation staff and completed 4 weeks of no training. They were then seen once more for assessment of all procedures described above.

Statistical Analysis

Statistical analysis software used were SuperANOVA and Statview (Abacus, Carmel CA). A one- way analysis of variance (ANOVA), having one within factor and one between factor, was used to examine the demographic variables of age, height (in centimeters [cm]), and weight (in kilograms [kg]). PwMS were matched with healthy subjects for gender and age ± one to two years. A repeated-measures ANOVA, with one within factor (time, having three levels: pretraining, posttraining and detraining) and one between factor (group, having two levels: the data of those with multiple sclerosis (MS) and the healthy subjects, (H) was used to examine the variables of maximal pressures, pulmonary function, maximal voluntary cough, airway resistance, and the questionnaire data. A repeated-measures ANOVA having two within subject factors for time (pretraining, posttraining and detraining) and sound pressure level (SPL) (having two levels: normal (N) and loud (L)) and one between factor, group (MS and H), was used to examine the acoustic and aerodynamic data of speech. A repeated-measures ANOVA, one within factor for time (pretraining, posttraining and detraining) and one between factor for group (MS and H) was used for the questionnaires.

When no group and time interaction was found, data was examined with main effects. If a main effect for a dependent variable was found a post hoc analysis (Bonferroni/Dunn) was performed. For variables with three levels, contrast by means comparisons were used to determine between the levels, which were significant. Significance level was set at a p-value ≤ 0.05. Means $\pm$ standard error (SE) are provided for variables of interest. An ANOVA table and linear graphic presentation, showing means and standard error of the data, follows each written description of the results. Within the graphic presentation SE bars are presented either upwards or downwards when the lines are close enough to have overlap.

Correlations were performed to determine the relationship, if any, between the variables. A correlation score of less then .25 shows little or no relation, .25 to .5 are fair, .5 to .75 is moderate to good, while values above .75 are considered good to excellent (137).

A multiple regression analysis was completed for all demographic variables to determine their relationship to MEP and delta MEP (change from pretrain to post train, pretrain to detrain, and post train to detrain). Simple regressions were completed on all dependent variables e.g. MIP, PFT, cough, and speech data, to determine the amount of variability in the change of each variable could be explained by the change in MEP (137). Data is present descriptively and with scatter plots including a regression line for the simple regressions.

CHAPTER 4
RESULTS

Demographics

Data were collected on 31 subjects. Demographic data, presented in Table 1, shows the participants separated into three groups (i.e., mild MS, moderate MS, and healthy controls). There were no statistical differences in age, height or weight of the groups. For the PwMS, data for years from first symptoms, years from diagnosis, level of disability, EDSS and FSS are presented in Table 2.

Table 1. Demographics of All Subjects

	Mild MS	Moderate MS	Healthy Controls
Gender	9 women, 1 man	5 women, 2 men	12 women, 2 men
Age, yr	48.2±2.1	49.9±3.5	44.1±2.0
Height, cm	164.28±2.54	171.63±3.45	165.75±1.96
Weight, kg	71.07±5.79	83.65±8.73	78.13±3.70

Maximal Respiratory Pressures

MEP

No interaction occurred between group and time. Main effects were found for group and time. Group means were 80.55 ± 2.99 and 130.66 ± 6.12 cm H_2O, for the MSc (combined data of those with mild and moderate disability) and H groups (healthy controls), respectively. A significant difference was found between the groups ($F = 23.93$, $p = 0.0001$). Time means were 85.73 ± 6.55, 114.73 ± 7.61, and 109.09 ± 6.75 for the pretraining, posttraining, and detraining assessments, respectively. Contrast was

Table 2 Years from 1st symptom, years from diagnosis, & EDSS and FS scores

Subject	Years from 1st symptom	Years from diagnosis	EDSS	Pyramidal	Cerebellar	Brainstem	Sensory	Bowel & Bladder	Visual	Cerebral	Other (spasticity)
1	21.50	1.25	2.5	2	1	0	2	0	0	0	0
2	5.25	4.75	2.5	0	2	0	0	1	2	0	1
3	11.50	11.00	2.5	1	1	2	2	1	1.5	0	1
4	6.00	3.50	3.0	3	2	1	2	2	0	0	1
5	5.00	3.50	3.0	1	1	1	1	2	2	1	1
6	8.25	8.00	3.0	2	2	2	2	3	0	0	1
7	1.25	1.25	3.0	2	1	1	1	0	0	0	1
8	13.75	1.25	1.5	1	1	1	0	1	0	0	0
9	8.00	5.25	3.0	3	1	0	1	1	1	0	0
10	24.25	16.25	3.5	2	3	2	1	1	3	0	2
11	10.00	5.25	5.0	3	2	2	0	4	0	0	1
12	18.00	17.00	6.0	3	2	1	2	3	2	0	3
13	15.75	15.50	4.0	0	3	2	2	3	1	1	0
14	4.25	3.50	4.5	4	2	2	3	3	0	0	2
15	18.25	18.00	4.0	3	3	3	0	2	0	0	2
16	16.00	15.00	6.5	4	3	4	1	3	2	0	3
17	13.00	13.00	4.0	3	3	1	0	2	0	0	1
MEAN	11.8	8.4	3.6								

Expanded Disability Status Scale (EDSS) of individuals with MS. EDSS score is based on the score achieved from the Functional Status (FS) score. There are 8 FS subscores which range from 0 to 5 or 6. The EDSS ranges from 0 to 10, its score is based on a composite of the FS, i.e., all 0's on FS is a 0 on the EDSS, where as having a 1 on any of the FS and all the rest 0's is a 1 on the EDSS.

used to test the means. A significant difference was found between pretrain and post train ($F = 95.01$, $p = 0.0001$) and between pretrain and detrain ($F = 60.99$, $p = 0.0001$). The ANOVA table is presented in Table 3. Figure 2 presents the changes seen in MEP between the MSc and H groups.

Table 3. Anova Table for MEP

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
group	1	57835.35	57835.35	23.93	.0001
Subject(Group)	29	70087.43	2416.81		
time	2	14783.01	7391.50	53.28	.0001
time * group	2	167.22	83.61	.60	.5507
time * Subject(...	58	8046.37	138.73		

Dependent: MEP

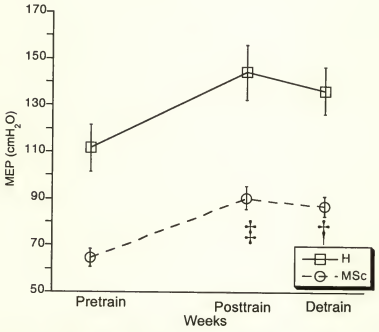

Figure 2. Change in MEP from pretrain through to detrain. A significant difference was found between the MSc and H groups and across assessments, between pretrain and posttrain (double vertical cross: ‡), as well as pretrain and detrain (dagger: †). Legend symbols are maintained throughout all graphs: MSc ⊖) and H ( ). Significance is at $p \leq 0.05$.

MEP was also analyzed with the MS data separated as to level of disability, (mild = Mi and moderate = Mo). A means contrast showed a significant differences between Mi and H ($F = 18.35$, $p = 0.0002$) and between Mo and H ($F = 13.20$, $p = 0.0011$). As in the analysis of MSc (MS data combined) and H groups there was a significant difference between pretrain and posttrain and between pretrain and detrain, with a trend toward significance between post train and detrain. Figure 3 presents the MS data separated by level of disability and the H group. Note, for clarity, in figures where the lines were extremely close and the error bars would lay on top of each other only the top or bottom error bar was presented.

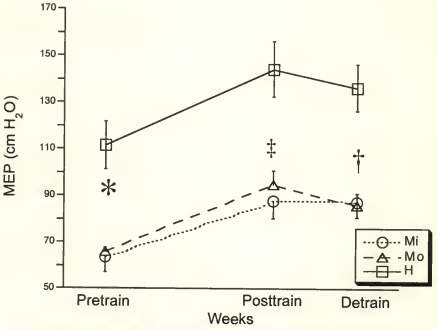

Figure 3. Change in MEP examined with the MS data separated as to level of disability (mild = Mi and moderate = Mo) from pretrain through to detrain. Significant difference was found between Mi & H and Mo & H groups. Significant difference was found between pretrain & posttrain (‡) and pretrain & detrain (†). Legend: Mi = O, Mo = Δ, and H = □. Significant group difference is marked by an asteric (*).

Within the MSc group there was an outlier, Mi patient number 9 who was a recreational singer and musician, whose MEP was 20 to 40 cm H_2O greater than all other participants. Removing this data point and rerunning the analysis lowered the mean for the MSc group to 61.81 ± 2.92 cm H_2O which continued to be significantly less than that of even the four lowest H participants (69.35 ± 4.71 cm H_2O) whose pretrain MEP were less than normal. Figures 2 and 3 include the data of this outlier.

Examination of percentage changes from pretraining to posttraining and from posttraining to detraining showed that the MSc group had a 40.4% gain from pretraining to posttraining and a 4.2% loss from posttraining to detraining. Examination of data based on level of disability shows that the Mi group improved 37.73% from pretraining to posttraining with no change from posttraining (87.53 cm H_2O) to detraining (87.30 cm H_2O). The Mo group increased 44.1% from pretraining to posttraining, but lost 9.46% from posttraining to detraining. The H group improved 29.2% pretraining to posttraining, but lost 5.44% from posttraining to detraining.

MIP

No interaction occurred between group and time. Significant main effects were found for group and time. Group means for MSc and H were 64.53 ± 2.90 and 91.57 ± 3.61 (cm H_2O), respectively. Time means were 72.27 ± 4.65, 79.05 ± 4.85, 78.90 ± 4.38 (cm H_2O) for pretrain, posttrain, and detrain assessments, respectively. Comparison of means found significant difference between pretrain and post train ($F = 10.34$, $p = 0.0021$) and between pretrain and detrain ($F = 9.08$, $p = 0.0038$). A moderate to good correlation, considered between .50 and .75, was found between MEP and MIP ($r = 0.738$, $p < 0.0001$) (137). Table 4 presents the ANOVA results for MIP for the combined

MS data (MSc) and the healthy controls. Figure 4 presents the data for MIP of the MSc and H groups.

Table 4. Anova of MIP for the MSc and H groups

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
group	1	16833.66	16833.66	12.62	.0013
Subject(Group)	29	38676.13	1333.66		
time	2	933.31	466.65	6.49	.0029
time * group	2	140.48	70.24	.98	.3827
time * Subject(...	58	4171.34	71.92		

Dependent: MIP

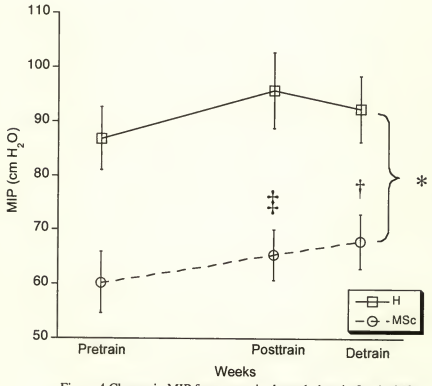

Figure 4 Change in MIP from pretrain through detrain for the MSc and H groups. Significant difference was found between the groups (*). Significant difference was found between pretrain & posttrain (‡) and between pretrain & detrain (†). Significance level is $p \leq 0.05$

MIP was also analyzed with the MS data separated as to level of disability, Mi and Mo, compared to H group. Group means for Mi and Mo were 58.59 ± 3.75 and 73.03 ± 3.99 (cm H_2O), respectively. Significant difference occurred between Mi and H

(F = 14.76, p-value = 0.0006). Time means for pretrain, post train, and detrain were identical to that of the combined data. Table 5 presents the ANOVA results for MIP with the MS data separated as to level of disability. Figure 5 presents MIP data for the MS subjects separated as to level of disability and the H group.

Table 5. MIP for Mi, Mo, and H groups

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Mi vs Mo vs HVC	2	19410.10	9705.05	7.53	.0024
Subject(Group)	28	36099.69	1289.27		
time	2	906.49	453.24	6.18	.0038
time * Mi vs Mo...	4	202.25	50.56	.69	.6026
time * Subject(...	56	4109.56	73.38		

Dependent: MIP

Examination of percentage changes from pretraining to posttraining and from posttraining to detraining showed that the MSc group had an 8.39% gain from pretraining to posttraining and a 3.9% gain from posttraining to detraining. Examination of data based on level of disability shows that the Mi group improved 6.66% from pretraining to posttraining with a further gain of 2.8% from posttraining to detraining. The Mo group increased 10.09% from pretraining to posttraining, with a further gain of 10.45% from posttraining to detraining. The H group improved 10.19% pretraining to posttraining, but lost 3.79% from posttraining to detraining.

Pulmonary Functions Tests

Pulmonary function variables were analyzed using both the actual data and the data normalized to percent of predicted. Within each section the results for the actual data are presented first, which is then followed by the results for the percent predicted.

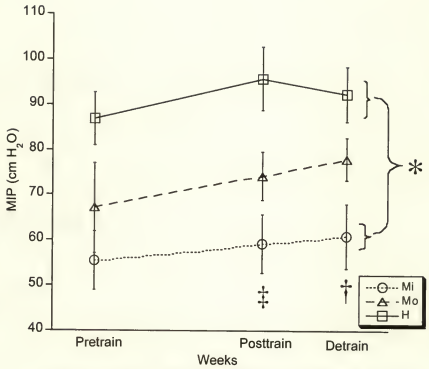

Figure 5. Change in MIP from pretrain through detrain for the Mi, Mo, and H groups. Significant difference was found between the Mi and H groups. Significant difference was found between pretrain & posttrain (‡) and pretrain & detrain (†). Significance is $p \leq 0.05$

FEV_1

No interaction or significant main effects were found for the actual data. However, analysis of FEV_1 normalized to percent of predicted found a group difference (F-value =9.85, p-value = 0.004). The means were 91.02± 2.15 and 107.33 ± 2.39 for the MSc and H groups, respectively. When the MS data was separated as to level of disability a significant difference was found for group (F value = 5.18, p-value = 0.0124). Contrasts by means comparison found a significant difference between the Mi and the H groups (F value = 9.72, p-value = 0.0043). Table 6 presents the ANOVA for the MSc and H groups. Figure 6 graphical shows the difference between the MSc and H group.

Table 7 presents the ANOVA for the Mi vs Mo vs H groups. Figure 7 graphical shows the difference between the MSc and H group.

Table 6. Anova Table for FEV_1 for MSc and H groups

Source	df	Sum of Squares	Mean Square	F-Value	P-Value	
MS vs H	1	5878.38	5878.38	9.85	.0040	
Subject(Group)	28	16705.82	596.64			
TIME	2	39.36	19.68	.34	.7162	.
TIME * MS vs H	2	271.93	135.97	2.32	.1076	.
TIME * Subject(...	56	3281.59	58.60			

Dependent: %FEV1

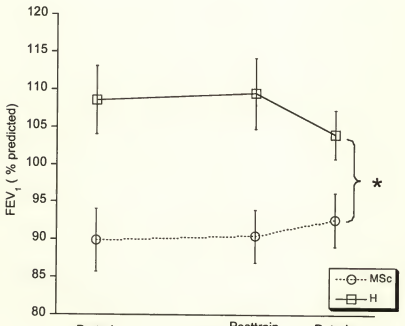

Figure 6. FEV_1 % of predicted for the MSc and H groups.
A significant main effect for group was found (*). Significance level is $p \leq 0.05$.

Table 7. Anova Table for %FEV1 for Mi vs Mo vs H groups

Source	df	Sum of Squares	Mean Square	F-Value	P-Value	
Mi vs Mo vs H	2	6265.44	3132.72	5.18	.0124	
Subject(Group)	27	16318.76	604.40			
TIME	2	3.71	1.86	.03	.9691	.
TIME * Mi vs M...	4	366.60	91.65	1.55	.2001	.
TIME * Subject(...	54	3186.92	59.02			

Dependent: %FEV1

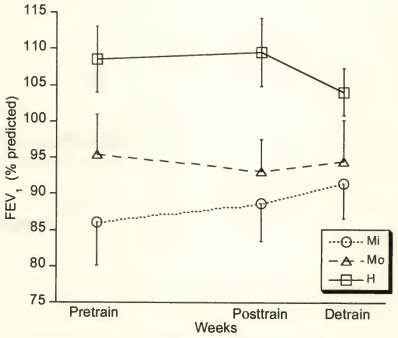

Figure 7. FEV_1 % of predicted for the Mi, Mo, and H groups. A significant main effect was found for group. A significant difference was found between the Mi & H group. Significance level is $p \leq 0.05$.

FVC

No interaction was found between group and time with the actual data or with the data normalized as to percent predicted. A significant main effect was found for group for the MSc compared to the H group, ($F = 4.84$, $p = 0.0363$). The group means were 3.27 ± 0.10 (l) and 3.84 ± 0.13 (l) for the MSc and H groups, respectively. Analysis of FVC normalized as to percent of predicted found no interaction, but a significant main effect for group with the MS data combined ($F = 13.20$, $p = 0.0011$) and separated as to level of disability ($F = 5.72$, $p = 0.0085$) compared to the healthy control group. Groups means were 95.94 ± 2.09 % of predicted and 114.90 ± 2.75 % of predicted for the MSc and H, respectively. Groups means were 95.42 ± 3.05 % of predicted and 96.68 ± 2.70 % of predicted for the Mi and Mo, respectively. Significant differences were found between

the Mi and the H groups ($F = 9.25$, $p = 0.0052$), as well as the Mo and the H groups ($F = 6.51$, $p = 0.0167$). Table 8 presents the ANOVA for the MSc and H groups. Figure 8 graphical shows the difference between the MSc and H group. Table 9 presents the ANOVA for the Mi vs Mo vs H groups. Figure 9 graphical shows the difference between the MSc and H group. Correlation analysis found a negative relationship between FVC and MEP ($r = -0.434$, $p < 0.0001$).

Table 8. Anova Table for FVC % of predicted for MSc and H groups

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
MS vs H	1	8615.91	8615.91	13.20	.0011
Subject(Group)	29	18927.87	652.69		
TIME	2	58.51	29.25	.50	.6081
TIME * MS vs H	2	239.74	119.87	2.06	.1374
TIME * Subject(...	57	3323.72	58.31		

Dependent: %FVC

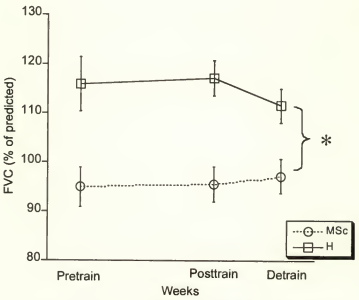

Figure 8. FVC % of predicted for the MSc and H groups. Significant main effect was found for group (*), $p < 0.05$.

Table 9. Anova Table for FVC % of predicted for Mi vs Mo vs H groups

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Mi vs Mo vs H	2	7961.95	3980.97	5.72	.0085
Subject(Group)	27	18782.81	695.66		
TIME	2	7.94	3.97	.07	.9369
TIME * Mi vs M...	4	276.12	69.03	1.14	.3497
TIME * Subject(...	54	3283.29	60.80		

Dependent: %FVC

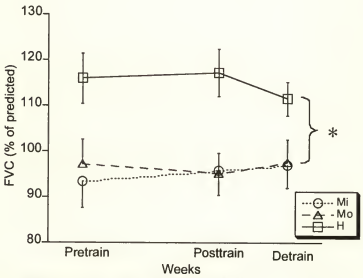

Figure 9. FVC % of predicted for the Mi, Mo, and H groups. Significant main effect was found for group (*), $p < 0.05$. The Mi and Mo groups were different from the H group, but not different from each other.

PEF

No interaction was found between group and time for the actual data. A significant main effect for group ($F = 13.39$, $p = 0.001$) was found between the MSc and H subjects for PEF. The group means were 5.73 ± 0.20 and 7.36 ± 0.21 (L/s) for the MSc and H subjects, respectively.

When the PEF data was analyzed with the data separated as to level of disability, Mi and Mo, significant main effects for group and time were found. The group means

were 5.30 ± 0.26 and 6.35 ± 0.25 (L/s), for the Mi and Mo groups, respectively. Contrast of the means was used to further analysis the relationship between the group means. A significant difference occurred between the Mi and H groups ($F = 14.76$, $p = 0.0006$). The time means were 6.16 ± 0.32, 6.62± 0.26, 6.53 ± 0.28, for the pretrain, posttrain, and detrain assessments, respectively. Comparison of the means found a significant difference between pretrain and post train ($F = 8.30$, p-value = 0.0056) and pretrain and detrain ($F = 10.14$, p-value = 0.0024). A moderate to good correlation was found between MEP and PEF ($r = 0.631$, $p < 0.0001$). Table 10 presents the ANOVA results for the PEF among the three groups. Figure 10 presents the change over time for the three groups. Note that Mi group continued to improve from post train to detrain while the Mo group decreased and the H group had no change.

Table 10. Anova Table for PEF between the Mi, Mo, and H groups

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Mi vs Mo vs HVC	2	72.24	36.12	8.98	.0010
Subject(Group)	27	108.57	4.02		
time	2	4.64	2.32	4.13	.0214
time * Mi vs Mo...	4	4.36	1.09	1.94	.1165
time * Subject(...	54	30.28	.56		

Dependent: PEF

Analysis of the PEF data normalized to percent of predicted found a trend toward an interaction (F-value = 2.71, p-value = 0.0754) and significant main effects group, MSc compared to H (F-value = 24.51, p-value = 0.0001) and for time (F-value = 3.09, p-value = 0.0531). Group means were 81.74 ± 2.48 % of predicted and 107.99 ± 2.44 % of predicted for the MSc and H groups, respectively. Time means were 89.18 ± 4.24 % of predicted, 96.74 ± 3.90 % of predicted, and 94.25 ± 3.34 % of predicted for the pretraining, posttraining and detraining assessment, respectively. Further analysis of time

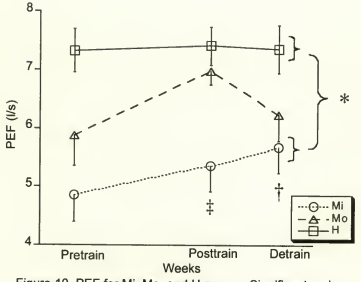

Figure 10. PEF for Mi, Mo, and H groups. Significant main effects were found for group and time. A significant difference was found between Mi and H groups (*). Significant difference was found between pretrain and posttrain (‡) and between pretrain and detrain (†). Significance level is p <0.05

by comparison of means found significant difference within the MSc between pretraining and posttraining (F-value = 8.03, p-value = 0.0063) and pretraining and detraining (F-value = 7.91, p-value = 0.0067). Significant difference was found between the two groups at each assessment: pretraining (F-value = 80.30, p-value = 0.0001), posttraining (F-value = 55.07, p-value = 0.0001) and detraining (F-value = 34.84, p-value = 0.0001). Table 11 presents the ANOVA for % of predicted for MSc compared to H. Figure 11 presents the change over time for the two groups.

Table 11. Anova Table for PEF % of predicted between MSc and H

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
MS vs H	1	15854.69	15854.69	24.51	.0001
Subject(Group)	29	18758.73	646.85		
TIME	2	589.78	294.89	3.09	.0531
TIME * MS vs H	2	516.01	258.01	2.71	.0754
TIME * Subject(Gr...	57	5436.54	95.38		

Dependent: %PEF

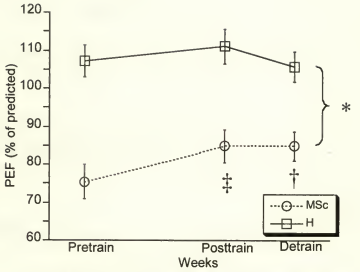

Figure 11. PEF % of predicted for MSc and H groups. Significant main effects were found for group and time. A significant difference was found between the groups (*) at each assessment. Significant differences were found between pretrain and posttrain (‡) and between pretrain and detrain (†). Significance level is $p < 0.05$.

Analysis of MS data separated as to level of disability compared to the H group found no interaction but significant main effects for group (F-value = 12.62, p-value = 0.0001) and time (F-value = 4.38, p-value = 0.0171). Group means were 78.98 ± 3.60 % of predicted, 85.68 ± 3.03 % of predicted and 107.99 ± 2.44 % of predicted for the Mi, Mo, and H groups, respectively. Further analysis found significant differences between the Mi and H groups (F-value = 22.70, p-value = 0.0001) and the Mo and H groups (F-value = 10.83, p-value = 0.0027). Time means were identical to those in the analysis of MSc compared to H group. Further analysis of the means by contrast found significant difference between pretraining and posttraining (F-value = 8.44, p-value = 0.0053) and a between pretraining and detraining (F-value = 3.85, p-value = 0.0547). Table 12 presents the ANOVA for % of predicted for PEF with MS data separated as to level of disability compared to H group. Figure 12 presents the change over time for the three groups.

Table 12. Anova Table for %of predicted for Mi, Mo, and H groups

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Mi vs Mo vs H	2	15101.31	7550.66	11.37	.0003
Subject(Group)	27	17938.03	664.37		
TIME	2	831.37	415.68	4.30	.0185
TIME * Mi vs M...	4	730.34	182.59	1.89	.1256
TIME * Subject(...	54	5218.95	96.65		

Dependent: %PEF

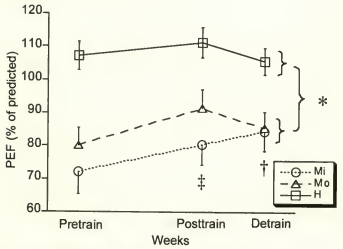

Figure 12. PEF % of predicted for the Mi, Mo, and H groups. Significant difference was found between the Mi and H & the Mo and H groups (*). Significant difference was found between pretrain and posttrain (‡) and pretrain and detrain (†). Significant level is $p < 0.05$.

Airway Resistance

Resonance frequency

No significant difference was found for the components of airway resistance (R(5Hz), R(20Hz), X(5Hz), IO VT, IO R central and IO R peripheral) except for resonance frequency. A significant interaction occurred between group (MSc and H) and time for resonance frequency. Means for the interaction of time and group were 12.25 ± 1.20, 13.18 ±1.12 for pretrain, MSc and pretrain, H; 14.44 ± 1.60 and 11.90 ±

0.81 for post train, MSc and post train H; and 15.01 ± 1.96 and 11.98 ± 0.87 for detrain, MSc and detrain, H, respectively. Contrasts by means comparison found significant difference between the MSc and H groups at posttraining (F-value =4.67, p-value = 0.0350) and at detrain (F-value = 6.57, p-value =.0350). Within the MSc group significant differences were found between pretraining and posttraining (F-value =3.88, p-value =.0537) and between pretraining and detraining (F-value =6.08, p-value =.0167) A correlation considered weak to having no relationship (0 to 0.25) was found between resonance frequency and MEP (137). The ANOVA results are shown in Table 13. The interaction is shown in Figure 13.

Table 13. Anova Table for Resonance Frequency for MSc and H groups

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
group	1	51.17	51.17	.83	.3707
Subject(Group)	29	1794.55	61.88		
time	2	8.88	4.44	.44	.6440
time * group	2	69.78	34.89	3.48	.0374
time * Subject(...	57	571.08	10.02		

Dependent: Resonance Frequency

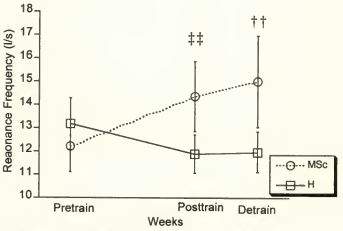

Figure 13. Resonance Frequency (l/s) for the MSc and H groups. An interaction was found between group and time. Contrasts by means comparison found significant difference between the MS and H groups at the posttrain (‡‡) and detrain (††) assessments. Significance level is p <0.05.

Maximal Voluntary Cough

Volume

No interaction of group and time was found. A significant main effect was found for group (F-value = 5.09, p-value = 0.0318). The group means were 1.70 ± 0.11 and 2.17 ±0.08 (L) for the MSc and H, respectively. A fair correlation was found between MEP and volume (r = 0.377, p = 0.0002). Table 14 presents the ANOVA results for volume. Figure 14 shows the difference between the groups' mean volumes at each assessment session.

Table 14. Anova Table for Volume for MSc and H groups

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
group	1	5.06	5.06	5.09	.0318
Subject(Group)	29	28.84	.99		
time	2	.30	.15	.96	.3906
time * group	2	.31	.16	1.01	.3721
time * Subject(...	58	9.05	.16		

Dependent: Volume

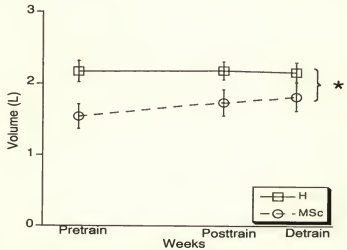

Figure 14. Cough volume changes in MSc and H groups from pretrain through detrain. Significant difference was found between the MSc and H group (*). Significance level is $p \leq 0.05$.

Additionally, when the MS subjects were separated as to level of disability (Mi = 1.52 ± 0.11 l and Mo = 1.95 ± 0.20 l) there was a significant difference between the Mi and H groups ($F = 7.75$, $p = 0.0095$), but not between either the Mi and Mo or Mo and H groups. Figure 15 presents the volume data separated as to level of disability and H groups.

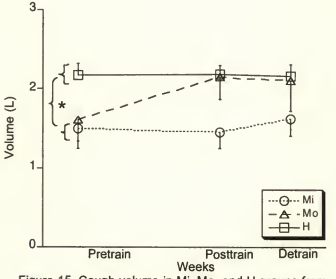

Figure 15. Cough volume in Mi, Mo, and H groups from pretrain through detrain. Significant difference was found between Mi and H groups (*). Significance level is $p \leq 0.05$.

Volume was also examined as a percent of FVC. The volume over the FVC for each subject at each assessment ([Vol/FVC] x 100) was calculated. The percentage was further examined by a 1-way repeated-measures ANOVA. No significant interaction or main effects were found. A moderate to good correlation was found between volume and FVC ($r = 0.594$, p 0.0001).

Cough air flow

No interaction was found between group and time nor mean effects for the MSc group compared to the H group. An interaction was found when the MS data separated as to level of disability was compared to the H group (F-value = 2.51, p-value = 0.0522). Group means for the interaction were: at pretraining 6.61 ± .35, 6.37 ± .89, and 7.33 ± .33 for the Mi, Mo, and H groups, respectively; at posttraining 6.20 ± .41, 7.37 ± 1.19, and 7.42 ± .41 for the Mi, Mo, and H groups, respectively; and at detraining 6.69 ± .55, 7.36 ± .98, and 7.24 ± .22 for the Mi, Mo, and H groups, respectively. Comparison of the means revealed significant differences at pretraining: Mi vs H (F-value = 5.44, p-value = 0.0233) and Mo vs H (F-value = 7.87 p-value = 0.0069) and at posttraining: Mi vs Mo (F-value = 5.44, p-value = 0.0233) and Mi vs H (F-value = 5.49, p-value = 0.0002). Significant difference in air flow was found for the Mo group between pretraining and posttraining (F-value = 6.35, p-value = 0.0146) and between pretraining and detraining (F-value = 6.24, p-value = 0.0155). A weak correlation was found between air flow and MEP (r = 0.241, p = 0.0197). Table 15 presents the ANOVA for flow for the Mi, Mo, and H groups. Figure 16 presents the flow data separated as to level of disability and H groups.

Table 15. Anova Table for Flow for the Mi, Mo and H groups

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Mi vs Mo vs HVC	2	12.10	6.05	.79	.4638
Subject(Group)	28	214.48	7.66		
time	2	1.60	.80	1.44	.2462
time * Mi vs Mo...	4	5.59	1.40	2.51	.0522
time * Subject(...	56	31.24	.56		

Dependent: Flow

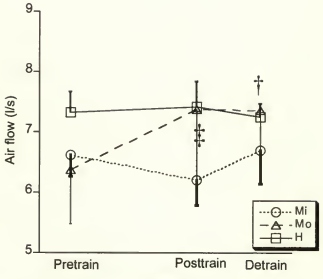

Figure 16. Air flow during cough for the Mi, Mo, and H groups. Comparison of means revealed significant difference in the Mo group from pretraining to posttraining (‡) and from pretraining to detraining (†). Significant differences were found between the Mi and H & the Mo and H groups pretraining and between the Mi and H & Mi and Mo groups at posttraining. Significance level is $p < 0.05$.

Flow was analyzed as a percentage of PEF ([flow/PEF] x 100). A main effect was found between MSc and H groups ($F = 5.33$, $p = 0.0282$). Group means were 121.4 ± 5.3 and 100 ±2.0 for the MSc and H groups, respectively. Table 16 presents the ANOVA for flow as a percent of PEF for the MSc and H groups.

Table 16. Anova Table for (Flow/PEF)*100 for the MSc and H groups

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Group	1	10321.84	10321.84	5.33	.0282
Subject(Group)	29	56116.56	1935.05		
time	2	1244.97	622.48	1.74	.1841
time * Group	2	947.84	473.92	1.33	.2733
time * Subject(...	58	20720.18	357.24		

Dependent: (Flow/PEF)*100

Analysis, with the MS data separated as to level of disability. A strong trend toward a significant interaction was found between group and time ($F = 2.47$, $p =$

0.0549), therefore this was further analyzed. At pretraining the means were 146.92, 107.04, and 100.88 for the Mi, Mo and H groups, respectively; at posttraining the means were 120.37, 104.04, and 99.82 for the Mi, Mo and H groups, respectively; and at detraining the means were 122.87, 115.10, and 99.86 for the Mi, Mo and H groups, respectively. Comparison of the means by contrast found significant difference between the Mi and H groups at pretraining (F-value = 37.59, p-value = 0.0001); at posttraining (F-value = 7.49, p-value = 0.0001); and at detraining (F-value = 9.39, p-value = 0.0033). A significant difference was found between the Mi and Mo groups at pretraining (F-value = 19.91, p-value = 0.0001). Within the Mi group there were significant differences from pretraining to posttraining (F-value = 16.71, p-value = 0.0018) and from pretraining to detraining (F-value = 8.79, p-value = 0.0044). A significant main effect was found for group (F-value = 4.38, p-value = 0.0221). Means comparison found a significant difference between the Mi and H group (F-value = 8.65, p-value = 0.0065). Table 17 presents the ANOVA for (flow/PEF)*100 for the Mi, Mo, and H groups. Figure 17 presents the data for (flow/PEF)*100 for the Mi, Mo, and H groups. Correlation analysis found a moderate to good relationship between flow and PEF ($r = .529$, $p < 0.0001$).

Table 17. Anova Table for (flow/PEF)*100 for the Mi, Mo, and H groups

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Separated grou...	2	15834.88	7917.44	4.38	.0221
Subject(Group)	28	50603.52	1807.27		
time	2	1441.34	720.67	2.19	.1213
time * Separate...	4	3250.03	812.51	2.47	.0549
time * Subject(...	56	18417.99	328.89		

Dependent: (Flow/PEF)*100

Rise Time

Rise time is the time period in msec from point A to point B (see Figure 1, in Chapter 3) which was the time to cross from the lower threshold, set at the baseline, to the upper threshold, set at the peak of the wave. No interaction between groups and times were found. A significant main effect for group was found. The group means were 73.04

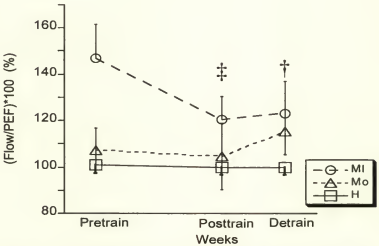

Figure 17. (Flow/PEF)*100 for the Mi, Mo, and H groups. An interaction occurred between group and time. Means comparison by contrast found significant difference between the Mi and H groups at each time period, between Mi and Mo at pretraining, and within the Mi group differences between pretraining and posttraining (‡) & pretraining and detraining (†). Significance level was $p < 0.05$.

± 7.28 and 44.28 ± 4.29, for the MSc and H groups, respectively. An increase in rise time is a negative response, indicating a longer time to reach peak value. Correlation analysis found a weak relationship between rise time and MEP ($r = -.245$, $p = 0.0175$). Table 18 presents the ANOVA results for rise time and Figure 18 graphically presents the data.

Table 18. Anova Table for rise time for the MSc and H groups

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
group	1	19055.56	19055.56	5.25	.0294
Subject(Group)	29	105239.04	3628.93		
time	2	2702.30	1351.15	1.36	.2639
time * group	2	1031.18	515.59	.52	.5972
time * Subject(...	58	57493.09	991.26		

Dependent: Rise time

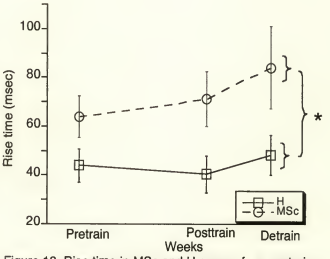

Figure 18. Rise time in MSc and H groups from pretrain through detrain. Significant difference was found betweem MSc and H groups (*). Significance level is $p \leq 0.05$.

Cough Volume Acceleration (CVA)

The CVA ($l/s*s^{-1}$) is the ratio of the peak amplitude (l/s) over the rise time (s) (40, 172). No interaction was found between groups and times. A main effect for group ($F = 6.60$, $p = 0.0156$) was found. The group means for the MSc and H groups were 130.75 ± 13.30 $l/s*s^{-1}$ and 217.93 ± 19.12 $l/s*s^{-1}$, respectively. Correlation analysis found a fair relationships between CVA and MEP ($r = .374$, $p = 0.0002$), between CVA and peak flow ($r = .473$, $p < 0.0001$) and moderate to good, but negative, relationship between

CVA and rise time ($r = -.659$, $p < 0.0001$). Table 19 and Figure 19 present the ANOVA results and a line graph for MSc and H data.

Table 19. Anova table for CVA for the MSc and H groups

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
group	1	175057.60	175057.60	6.60	.0156
Subject(Group)	29	769260.67	26526.23		
assessment	2	15082.15	7541.07	1.49	.2331
assessment * gr...	2	4909.98	2454.99	.49	.6175
assessment * S...	58	292886.48	5049.77		

Dependent: cough volume acceleration (L/s*s)

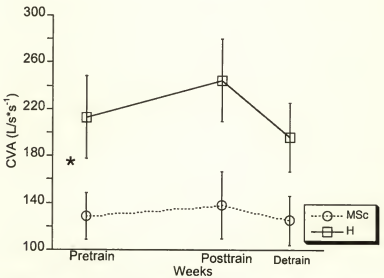

Figure 19. CVA for the MSc and H groups. A significant group difference was found between the MSc and H group (*). Significance level is $p < 0.05$

Leading Slope.

No interaction was found. A significant main effect was found for group. Group means for slope were 0.12 ± 0.01 and $0.17 \pm 0.01 (l/s*s^{-1})$ for the MSc and H groups, respectively. Correlation analysis found a fair relationship between leading slope and MEP ($r = .388$, $p = 0.0001$). Table 20 presents the ANOVA for leading slope. Figure 20 present the leading slope data for the MSc compared to the H group.

Table 20. Anova table for leading slope for MSc and H groups

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
group	1	.05	.05	5.14	.0311
Subject(Group)	29	.29	.01		
time	2	2.89E-3	1.45E-3	.61	.5468
time * group	2	4.11E-3	2.06E-3	.87	.4253
time * Subject(...	58	.14	2.37E-3		

Dependent: Leading slope

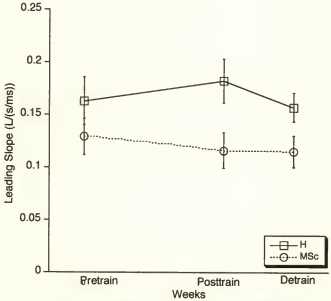

Figure 20. Leading slope was significantly different between the MSc and H groups (*). Significance level is $p \leq 0.05$.

Cough Compression

Cough compression was the time from the beginning of the cough compression phase to the end of this phase and the initiation of the exhalation phase. No interaction between groups and times or main effects for groups and times were found. Correlation analysis found a fair, but negative, relationship between cough compression and MEP ($r = -.364$, $p = 0.0003$).

Index of Pulmonary Dysfunction (IPD)

No interaction was found. A main effect for group occurred for the MSc group compared to the H group. The group means were 5.65 ± 0.19 and 4.23 ± 0.11, for the MSc and H participants, respectively. Table 21 presents the ANOVA for IPD for the MSc and H groups.

When the MS data was separated as to level of disability significant difference was found between the Mi, Mo, and H groups. The group means were 5.67 ± 0.20 and 5.62 ± 0.38, for the Mi and Mo, respectively. Table 22 presents the ANOVA table for IPD with the Mi, Mo, and H groups. Means comparison showed a significant difference between the Mi and H group ($F = 11.53$, $p = 0.0021$) and the Mo and H group ($F = 8.68$, $p = 0.0066$).

Correlation analysis found a fair, but negative relationship between IPD and MEP ($r = -.365$, $p = 0.004$). Figure 21 presents the data for IPD for the Mi, Mo, and H groups. The units for the Y axis in Figure 21 are integers as the IPD scale ranges from a normal score of 4 to severe respiratory dysfunction with a score of 11.

Table 21. Anova Table for IPD for the MSc and H groups

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
group	1	44.33	44.33	15.15	.0006
Subject(Group)	28	81.90	2.93		
time	2	1.22	.61	1.09	.3442
time * group	2	.02	.01	.02	.9837
time * Subject(...	56	31.38	.56		

Dependent: Pulmonary Index

Table 22. Anova table for IPD for Mi, Mo, and H groups.

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Mi vs Mo vs HVC	2	44.36	22.18	7.31	.0029
Subject(Group)	27	81.88	3.03		
time	2	1.33	.66	1.14	.3258
time * Mi vs Mo...	4	.13	.03	.06	.9941
time * Subject(...	54	31.27	.58		

Dependent: Pulmonary Index

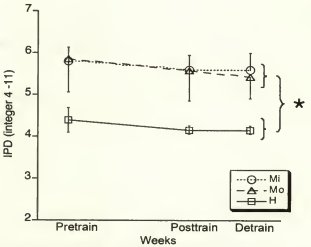

Figure 21. Change in IPD of Mi, Mo, and H groups from pretrain through detrain. Improvement is shown by a decrease in score (i.e., 7 going to 6). Significant difference was found between the Mi & H and Mo & H groups (*). Significance level is $p \leq 0.05$.

Speech

Acoustic components

A 3-way repeated measures ANOVA was used to analysis the acoustic data. Variables of interest are group (MSc & H, or Mi, Mo, & H); time (pretrain, posttrain, and detrain) and sound pressure level (normal [N] & loud [L]).

Vowel prolongation

No interaction was found for group, sound pressure level (SPL) here after known as loudness level, and time. An interaction did occur between group and time (F-value =

19.07, p-value =0.0001) and between loudness and group (F-value = 4.26, p-value =0.0481). The means for the interaction between group and time were 12.15 ± 0.74 and 14.65 ± 0.81 at pretraining for the MSc and H groups, respectively; 12.41 ± .74 and 17.62 ± 1.43 at posttraining for the MSc and H groups, respectively; and 15.14 ± 1.20 and 21.64 ±1.72 at detraining for the MSc and H groups, respectively. The means for the interaction between loudness and group were 12.81 ± .69 and 16.75 ± 1.05 at N loudness for MSc and H groups, respectively and 13.63 ± .84 and 19.11 ± 1.30 at L loudness for MSc and H groups, respectively. Table 23 presents the 3-way Anova for MSc compared to H group.

The means comparison results for the interaction between time and group were: F-value = 5.26, p-value = 0.0255 at pretraining; F-value 15.79, p-value = 0.0002 at posttraining, and F-value = 36.24, p-value = 0.0001 at detraining, respectively between the MSc and H groups. Within the MSc group significant differences were found between pretraining and detraining (F-value = 5.91, p - value = 0.0182) and between posttraining and detraining (F-value = 4.37, p - value = 0.0410). Within the H group significant difference were found between pretraining and postttraining (F-value = 3.97, p - value = 0.0510), between pretraining and detraining (F-value = 35.96, p - value = 0.0001), and between posttraining and detraining (F-value = 14.03, p - value = 0.0004).

The means comparisons for the interaction between loudness and group were F-value = 22.20, p - value = 0.0001 and F-value = 59.17, p - value = 0.0001 at the N and L level between the MSc and H groups. Within the H group there was a significant difference between the N and L level (F-value = 12.38, p - value = 0.0015). Figure 22

presents the interaction between time and group. Figure 23 presents the interaction between loudness and group.

Table 23 Anova Table for Vowel prolongation of MSc and H groups

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
group	1	977.67	977.67	7.23	.0118
Subject(Group)	29	3921.53	135.23		
time	2	696.56	348.28	19.07	.0001
time * group	2	146.23	73.11	4.00	.0235
time * Subject(Group)	58	1059.19	18.26		
Volume	1	122.20	122.20	10.05	.0036
Volume * group	1	51.79	51.79	4.26	.0481
Volume * Subject(Group)	29	352.73	12.16		
time * Volume	2	67.98	33.99	1.56	.2188
time * Volume * group	2	13.73	6.87	.32	.7306
time * Volume * Subject(Gr...	54	1174.30	21.75		

Dependent: vowel duration

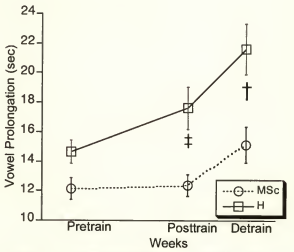

Figure 22. Vowel prolongation for the MSc and H groups. An interaction was found between time and group. Significant differences were found between the groups at each assessment. For the H group significant differences were found between pretraining and posttraining (‡) & between pretraining and detraining (†).

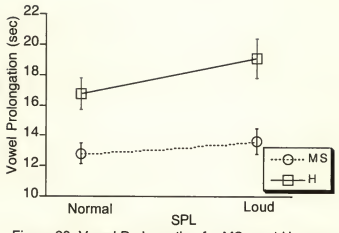

Figure 23. Vowel Prolongation for MSc and H group showing interaction between loudness and group. Differences were found between the MSc and H groups at the N andat the L level and in the H group between the N and L level. Significance is at $p < 0.05$

The vowel prolongation data was also examined with the MS data separated as to level of disability (i.e., Mi and Mo) compared to the H group. No interactions were found, however main effects were found for group, time and volume. The means for the groups were 14.23 ± 0.75 sec, and 12.54 ± 0.78 sec, 17.56 ± 0.84 sec for the Mi, Mo, and H group, respectively. The means for the time were 13.28 ± 0.56 sec, and 14.75 ± 0.83 sec, 18.07 ± 1.09 sec for the pretraining, posttraining, and detraining, respectively. The means for loudness were 14.59 ± 0.63 sec, and 16.10 ± 0.79 sec for the N and L, respectively. Means comparison by contrast found significant difference between the Mi and H groups ($F = 4.49$, $p = 0.0432$) and between the Mo and the H groups ($F = 5.48$, $p = 0.0266$). Means comparison by contrast for time was not possible. Table 24 presents the ANOVA for vowel prolongation for the Mi, Mo, and H groups.

Table 24. Anova table for vowel prolongation for the Mi, Mo, and H groups

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Mi vs Mo vs HVC	2	1010.16	505.08	3.63	.0396
Subject(Group)	28	3895.00	139.11		
time	2	472.97	236.49	12.97	.0001
time * Mi vs Mo...	4	173.57	43.39	2.38	.0624
time * Subject(...	56	1020.82	18.23		
Volume	1	79.88	79.88	6.37	.0175
Volume * Mi vs ...	2	54.12	27.06	2.16	.1343
Volume * Subjec...	28	350.92	12.53		
time * Volume	2	44.93	22.46	1.01	.3727
time * Volume *...	4	26.81	6.70	.30	.8765
time * Volume *...	52	1161.23	22.33		

Dependent: vowel duration

'My Grandfather' passage words per minute

The words per minute (WPM) is product to the number of words in the passage divided by the time to read the passage times 60 sec/min, i.e., (200 words per passage / 45 sec to read the passage) x (60 sec / min). No 3-way interaction was found between group, loudness and time for the MSc and the H groups. Three two way interactions were found 1) group x time, 2) loudness x group, and 3) time x loudness. Group x time interaction means were 175.44 ± 4.79 and 211.36 ± 3.87 at pretraining for the MSc and the H groups, respectively; 177.26 ± 5.16 and 204.79 ± 4.77 at posttraining for the MSc and the H groups, respectively; and 179.26 ± 4.89 and 202.68 ± 3.88 at detraining for the MSc and the H groups, respectively. Means comparison by contrast found significant differences between the two groups at each assessment: F-value = 268.90, p-value = 0.0001 at pretraining, F-value = 125.76, p-value = 0.0001 at posttraining, and F-value = 83.0, p-value = 0.0001 at detraining. Within the MS group there was a significant difference between pretraining and detraining (F-value = 5.62, p-value =

0.0211). Within the H group there were significant differences between pretraining and posttraining (F-value = 8.21, p-value = 0.0058) and between pretraining and detraining (F-value = 14.32, p-value = 0.0004).

Loudness x group interaction means were 176.90 ± 3.86 and 208.36 ± 3.48 for the MSc and H groups at N loudness and 177.62 ± 4.17 and 204.29 ± 3.42 for the MSc and H groups at L loudness, respectively. Means comparison by contrasts found significant difference between the two groups at N loudness (F-value = 553.53, p-value = 0.0001) and at L loudness (F-value = 376.94, p-value = 0.0001). Within the H group a significant difference was found between the N and L loudness (F-value = 9.45, p-value = 0.0046).

Time x loudness interaction means were 186.77 ± 5.14 and 196.55 ± 5.76 at pretraining for the N and L loudness, respectively; 200.89 ± 5.97 and 180.77 ± 4.776 at posttraining for the N and L loudness, respectively; and 187.84 ± 4.77 and 193.18 ± 5.16 at detraining for the N and L loudness, respectively. Means comparison could not be estimated for this analysis. Table 25 presents the ANOVA for WPM for the MSc and H groups. Figures 24 and 25 shows the interaction of group and time and the interaction loudness and group, respectively for the MSc and H groups.

WPM data was also analyzed with the MS data separated as to level of disability, Mi and Mo. No three way interaction was found. Three two-way interactions were found between group x time, group x loudness, and time x loudness. Group x time interaction means were 172.15 ± 4.50, 180.14 ± 9.41, and 211.36 ± 3.867 at pretraining for the Mi, Mo, and H groups, respectively. Means comparison by contrasts found significant difference between the Mi and H groups at pretraining (F-value =239.13,

p-value = 0.0105), at posttraining (F-value =104.44, p-value = 0.000), and at detraining (F-value =66.18, p-value = 0.0001); and between the Mo and H groups at posttraining (F-value =34.87, p-value = 0.0001) and at detraining (F-value =39.10, p-value = 0.0001). Within the Mi group there was a difference between pretraining and detraining (F-value =5.36, p-value = 0.0243). Within the H group differences were found between pretraining and posttraining (F-value =8.06, p-value = 0.0063) and between pretraining and detraining (F-value = 14.06, p-value = 0.0004).

Loudness x group interaction means were 175.21 ± 4.13, 179.25 ± 7.36, and 208.26 ± 3.45 at N loudness for the Mi, Mo, and H groups, respectively; and 175.75 ± 4.42, 180.25 ± 7.99, and 204.29 ± 3.42 for L loudness for Mi, Mo, and H groups, respectively. Means comparison by contrasts for the loudness x group interaction found significant difference between Mi and Mo at N loudness (F-value = 9.52, p-value = 0.0045) and at L loudness (F-value = 9.90, p-value = 0.0039); between Mi and H at N loudness (F-value = 440.13, p-value = 0.0001) and at L loudness (F-value = 336.12, p-value = 0.0001); and between Mo and H at N loudness (F-value = 251.53, p-value = 0.0001) and at L loudness (F-value = 161.28, p-value = 0.0001). Within the H group a significant difference was found between the N and L loudness (F-value = 9.12, p-value = 0.0053).

Time x loudness interaction means were 186.77 ± 5.14 and 196.55 ± 5.76 at pretraining for the N and L loudness, respectively; 200.89 ± 5.97 and 180.77 ± 4.66 at posttraining for the N and L loudness, respectively, and 187.8 ± 4 ± 4.77 and 193.18 ± 5.16 at detraining for the N and L loudness, respectively. Means comparison by contrast could not estimate the significant differences in the interaction of time x loudness.

Table 25. Anova table for WPM for the MSc and H groups

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
group	1	34371.88	34371.88	10.65	.0028
Subject(Group)	29	93626.11	3228.49		
time	2	133.10	66.55	.90	.4108
time * group	2	1484.85	742.43	10.08	.0002
time * Subject(Group)	58	4272.28	73.66		
speech intensity	1	61.73	61.73	1.76	.1954
speech intensity * group	1	281.12	281.12	8.00	.0084
speech intensity * Subject(Group)	29	1019.32	35.15		
time * speech intensity	2	6849.68	3424.84	30.42	.0001
time * speech intensity * group	2	270.08	135.04	1.20	.3095
time * speech intensity * Subject(Gro...	52	5854.24	112.58		

Dependent: WPM gp

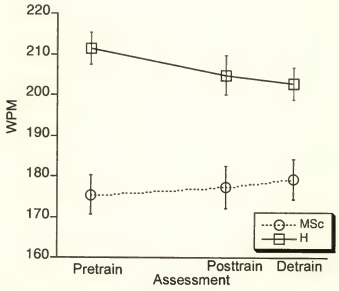

Figure 24 . WPM for the MSc and H groups showing the interaction of time and group. Significant difference was found between the groups at each assessment. Significance level is $p < 0.05$.

Table 26 presents the ANOVA for WPM for the Mi, Mo, and H groups.

Aerodynamic Component

Repetition of 'Pa'

Due to calibration issues data was examined by analyzing the relative difference

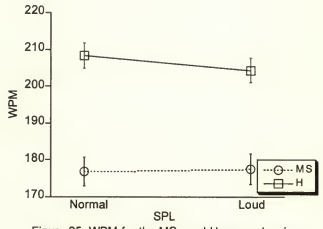

Figure 25. WPM for the MSc and H group showing interaction of group and loudness. Significant difference was found between the groups at both loudness levels. Significance is $p < 0.05$.

Table 26. Anova table for WPM for the Mi, Mo, and H groups

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Mi vs Mo vs HVC	2	35069.08	17534.54	5.25	.0115
Subject(Group)	28	93440.25	3337.15		
time	2	24.04	12.02	.16	.8523
time * Mi vs Mo vs HVC	4	1522.30	380.58	5.07	.0015
time * Subject(Group)	56	4199.85	75.00		
speech intensity	1	5.80	5.80	.16	.6929
speech intensity * Mi vs Mo...	2	281.07	140.53	3.86	.0331
speech intensity * Subject(...	28	1019.41	36.41		
time * speech intensity	2	5487.14	2743.57	23.98	.0001
time * speech intensity * M...	4	402.62	100.66	.88	.4829
time * speech intensity * S...	50	5721.70	114.43		

Dependent: WPM gp

in mV between each evaluation period. A 3-way repeated measures ANOVA, having two within factors, loudness and time and one between factor, group, was used to analyze the aerodynamic data. No 3-way interaction was found, however an interaction occurred between loudness, listed in the ANOVA table as speech intensity, and time. Analysis of the MS data separated as to level of disability found similar results with a significant interaction between time and volume (F-value = 6.81, p-value = 0.0031). Table 27

presents the ANOVA table for repetition of 'pa' for the MSc and H groups. Figure 26 presents the data for the repetition of 'pa' for the MSc and H groups.

Table 27. Anova table for the repetition of 'pa' for the MSc and H groups

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
group	1	.56	.56	.17	.6819
Subject(Group)	29	94.62	3.26		
time	2	32.35	16.17	22.05	.0001
time * group	2	.81	.40	.55	.5802
time * Subject(...	52	38.14	.73		
Volume	1	5.18	5.18	14.16	.0008
Volume * group	1	.01	.01	.02	.8957
Volume * Subjec...	27	9.87	.37		
time * Volume	2	10.36	5.18	6.57	.0035
time * Volume *...	2	.04	.02	.02	.9764
time * Volume *...	38	29.97	.79		

Dependent: relative change in Pah

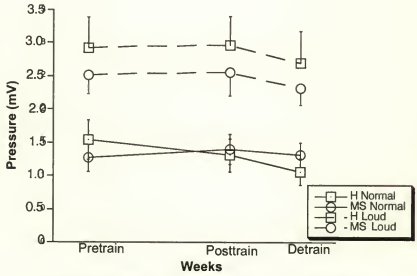

Figure 26. Repetition of 'pa' for the MSc and H groups. An interaction was found between the time, i.e. assessment periods and the loudness, N and L. Significance level is $p < 0.05$

Questionnaires

Dysarthria scale

No interaction was found between group and time for the MSc and H groups. A significant difference was found between the MSc and H groups ($F = 13.32$, $p = 0.0011$). Group means were 9.49 ± 0.11 and 10.00 ± 0.00 for MSc and H, respectively.

Analysis of the data for the Mi, Mo, and H groups found a significant interaction between group and time. Means for the interaction were 9.40 ± 0.27, 8.71 ± 0.47, and 10.00 ± 0.00 for pretraining, Mi, Mo, and H, respectively; 9.90 ± 0.10, 9.57 ± 0.20, and 10.00 ± 0.00 for posttraining Mi, Mo, and H, respectively; and 9.50 ± 0.27, 9.71 ± 0.18, and 10.00 ± 0.00 for detraining, Mi, Mo, and H groups, respectively. Means comparison by contrasts found significant difference between the Mi and H at pretraining ($F = 7.24$, $p = 0.0095$) and at detraining ($F = 5.03$, $p = 0.0290$) and between the Mi and Mo group at pretraining ($F = 6.89$, $p = 0.0112$). Within the Mi group there was a significant difference from pretraining to posttraining ($F = 4.45$, $p = 0.0396$). Within the Mo group significant differences were found between pretraining and posttraining ($F = 9.15$, $p = 0.0038$) and between pretraining and detraining ($F = 12.46$, $p = 0.0009$). Correlation analysis found a fair relationship between MEP and speech as assessed by the Dysarthria scale ($r = .287$, $p = 0.0058$). Table 28 presents the ANOVA table for the Dysarthria Scale data for Mi, Mo, and H groups. Figure 27 presents the Dysarthria scale data for the Mi, Mo, and H groups.

Table 28. Anova table for Dysarthria Scale for the Mi, Mo, and H groups

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Mi vs Mo vs HVC	2	6.62	3.31	7.98	.0019
Subject(Group)	27	11.20	.41		
time	2	3.25	1.63	5.78	.0053
time * Mi vs Mo...	4	3.34	.83	2.97	.0273
time * Subject(...	54	15.17	.28		

Dependent: dysarthria scale

Voice Related Quality of Life (VRQOL)

Three scores are derived for the VRQOL, i.e., total score (VT), social (VS), and physical (VP). For the VT no interaction was found between groups and times. A main effect for group was found between the MSc and H groups ($F = 9.11$, $p = 0.0054$). Group means for the MSc and H groups were 85.42 ± 2.27% and 98.21 ± 0.55%, respectively. When VT data was separated as to level of disability a main effect for group was found between the Mi, Mo and H groups ($F = 4.82$, $p = 0.0163$). The group means for the Mi and Mo groups were 87.30 ± 2.57% and 82.74 ± 4.12%, respectively. There were significant differences between Mi and H ($F = 5.02$, $p = 0.0335$) and between Mo and H ($F = 8.13$, $p = 0.0082$). Correlation analysis found a fair relationship between MEP and VT ($r = .391$, $p = 0.0001$) and a moderate to good relationship between DS and VT ($r = .533$, $p < 0.0001$). Table 29 presents the ANOVA for VT.

For the VS no interaction was found between groups and times. No main effects were found for group or time with the MSc compared to H group. When the MS data, separated as to level of disability, was compared to the H group, a significant main effect for group was found. A means comparison showed a significant difference between the Mo and H group ($F = 5.27$, $p = 0.0301$). Group means for VS were 92.96 ± 3.15%, 86.21

± 4.35%, and 99.36 ± 0.45% for Mi, Mo, and H groups, respectively. Correlation analysis found a fair relationship between MEP and VS (r = .272, p =0.0097) and a moderate to good relationship between DS and VS (r =.505, p < 0.001).

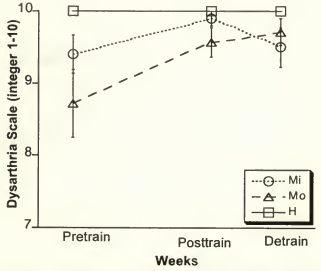

Figure 27. Dysarthria scale results for the Mi, Mo, and H groups. An interaction was found between group and time. Significant difference was found between Mi and H groups at pretraining and detraining and between Mi and Mo at pretraining. Mi dysarthria score was different from pretraiing to posttraining, while the Mo score was different between pretraining and posttraiining and between pretraining and detraining. Significance level is p < 0.05.

Table 29. Anova table for VT for MSc and H groups

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
group	1	3611.57	3611.57	9.11	.0054
Subject(Group)	28	11101.05	396.47		
time	2	81.57	40.79	.96	.3893
time * group	2	5.52	2.76	.06	.9372
time * Subject(...	56	2380.71	42.51		

Dependent: VRQoL

For the VP no interaction was found between group and time. A main effect for group was found between the MSc and the H group (F = 12.76, p = 0.0014). Group

means were 81.81± 2.36% and 97.01 ± 0.94% for MSc and H groups, respectively. When the MS data, separated as to level of disability, was compared to the H group a significant difference was found ($F = 6.18$, $p = 0.0052$). Means comparison found significant difference between the Mi and H ($F = 8.88$, $p = 0.0060$) and between the Mo and H ($F = 8.95$, $p = 0.0059$) groups. Group means were 82.40 ± 2.92%, 81.04 ± 3.95%, 97.01 ± 0.94% for the Mi, Mo, and H groups, respectively. Correlation analysis found a fair relationship between MEP and VP ($r = .454$, $p < 0.0001$) and a moderate to good relationship between DS and VP ($r = .500$, $p < 0.0001$). Table 30 presents the ANOVA for VP for the Mi, Mo, and H groups. Figure 28 presents the data for VP for VP for the Mi, Mo, and H groups.

Table 30. Anova Table for VP for the Mi, Mo, and H groups

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Mi vs Mo vs HVC	2	5006.63	2503.32	6.44	.0052
Subject(Group)	27	10495.52	388.72		
time	2	102.10	51.05	.85	.4332
time * Mi vs Mo...	4	77.57	19.39	.32	.8614
time * Subject(...	53	3183.71	60.07		

Dependent: VRQoL Physical

Regression Analysis

Multiple regression

MEP, as the dependent variable, was compared to the following predictor variables: group (MSc vs H and Mi vs Mo vs H), gender (female and male), age, and for the MS subjects - years from first symptom, years from diagnosis, and EDSS scores. Group and gender, nominal variables, were converted to categorical variables, i.e., X_1: MSc = 1 and H = 0; X_2: Mi =1 and Mo = 0; X_3: F = 1 and M = 0 (137). Proportion of

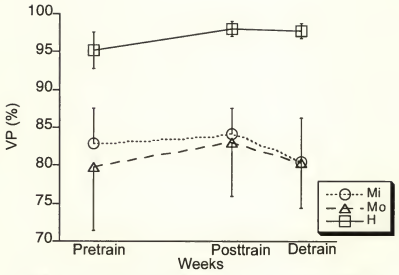

Figure 28. VP for the Mi, Mo, and H groups. Significant difference was found between the Mi and H & between the Mo and H. Significance level is $p < 0.05$.

variable of MEP, explained by the independent variables was found to be R_2 equal to .423 and adjusted R_2 equal to .404. Group and gender were found explain the variability in MEP at significant levels, whereas age did not. Table 31 presents the ANOVA table for the multiple regressions of MEP as the dependent variable and group (MSc vs H) and gender as independent variables. Table 32 presents the regression coefficients for MEP as the dependent variable and group and gender as independent variables.

A multiple regression analysis examined the association between MEP and level of disability (Mi and Mo, dummy variable X_2), EDSS score, years from first symptom, years from diagnosis, gender (dummy variable X_3), and age. Change in MEP was explained at significant level by years from 1st symptom (coefficient = -1.294, p-value = 0.0302) and age (coefficient = 1.434, p-value =0.0022). A second regression using only years from 1st symptom and age found that years from 1st symptom was the only

significant factor in relation to MEP Proportion of variable of MEP explained by the independent variables was found to be R_2 equal to 0.294 and adjusted R_2 equal to .286.

Table 30. ANOVA for multiple regression of MEP, group, and gender

	DF	Sum of Squares	Mean Square	F-Value	P-Value
Regression	2	63524.499	31762.249	32.759	<.0001
Residual	90	87261.782	969.575		
Total	92	150786.281			

Table 31. Regression Coefficients of group (MSc and H) and gender used in multiple regression with MEP, the dependent variable

	Coefficient	Std. Error	Std. Coeff.	t-Value	P-Value
Intercept	148.909	8.934	148.909	16.667	<.0001
X1 group	-50.826	6.495	-.628	-7.826	<.0001
X3 gender	-21.287	8.788	-.194	-2.422	.0174

As years from 1st symptom was the only one that was found significant, therefore a paired t-test was performed ($t = -27.222$, and $p < 0.0001$). Table 32 presents the ANOVA table for the multiple regressions for Mi and Mo. Table 33 presents the coefficients of the multiple regressions for Mi and Mo.

Table 32. ANOVA table for multiple regression of years from 1st symptom and age compared to MEP in Mi and Mo groups.

	DF	Sum of Squares	Mean Square	F-Value	P-Value
Regression	1	44339.588	44339.588	37.905	<.0001
Residual	91	106446.693	1169.744		
Total	92	150786.281			

Table 33. Regression coefficients of independent variables, years to 1st symptom and age, to dependent variable MEP for the Mi and Mo groups

	Coefficient	Std. Error	Std. Coeff.	t-Value	P-Value
Intercept	113.867	22.871	113.867	4.979	<.0001
Yrs 1st symp	-2.988	.527	-.558	-5.667	<.0001
age	.184	.511	.035	.360	.7198

Simple Regression

The change in each variable of interest (the dependent variables) were examined as their linear relationship to the change in MEP (the independent variable). A significant relationship was found between delta rise time and delta MEP (delta MEP = -.848, R = 0.373, R^2 = 0.139, F-value = 4.686, p-value < 0.0388). Figure 29 shows the simple regression with regression line for delta rise compared to delta MEP

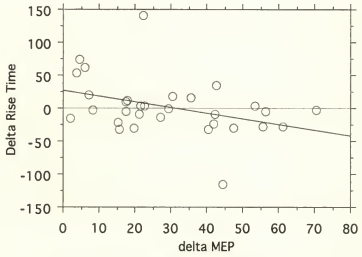

Figure 29. Simple regression of rise time for MSc and H groups

CHAPTER 5
DISCUSSIONS AND CONCLUSIONS

Maximal Pressures

MEP

Dependent on the nature of multiple sclerosis and its severity, respiratory muscle strength may be reduced to a variable extent. Prior to training the MEP of PwMS compared to norms was less than predicted for age and gender (10, 145). Prior to EMST PwMS had similar to or slightly higher MEP in comparison to other patients with neuromuscular disease (10, 11). Black and Hyatt (11) reported a range in the observed MEP from 35 to 190 and a range in the percent of predicted mean from 27% to 82% of with the overall mean being 47% of predicted. Garcia Rio et al (47), reported normal MEP in those with mild disability do to myasthenia gravis (MG) compared to those with moderate disability due to myasthenia gravis. MEP of PwMS following EMST was within the low to mid normal values for age and gender (10, 145). Normal MEP value was not present in all our healthy controls.

Individuals without neuromuscular dysfunction may present with muscle weakness. Four of the controls presented with expiratory muscle strength (EMS) less than the normal values (10, 145). EMST resulted in a mean MEP increase of 52%, in these four controls. This increase was greater then the percent increase of the PwMS, in our study and in pervious studies of PwMS receiving respiratory muscle strength training, as well as the overall increase of all healthy controls (52, 83, 131, 168, 189). On average

the PwMS and the healthy controls that displayed expiratory muscle strength substantially below normal had the greatest gains following EMST.

Previous investigators suggested the diminished strength of the expiratory muscles in PwMS may be due to deconditioning (131, 168). Deconditioning of the expiratory muscles may occur because their usual stimulus, strenuous activity, is often severely limited because of the heat sensitivity, fatigue, general muscle weakness, or balance problems associated with MS. In the current study all participants indicated they were affected by the fatigue of MS, with 58% of the participants reporting use of medication to combat their fatigue. Reduced extremity and trunk muscular strength, ranging from fair to good, was present in 88% of our subjects. However, no correlation has been found between the severity of the neuromuscular disease, as assessed by a general muscle index, and maximal respiratory pressures (182). In the current study five of six participants who were in a swim program once to twice per week had similar MEPs to that of the other participants. However, the sixth participant involved in a swim program had a baseline MEP of 83 cmH_20, this being approximately 27% greater than the other participants. Impaired balance was present in all our participants, ranging from very mild (e.g., abnormal signs without disability) to moderate (e.g., interferes with function). Spasticity, a velocity-dependent increase in muscle tone with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex may limit gains in strength (108). Thirteen of our participants were limited by spasticity (e.g., 8 mild, 3 moderate, and 2 severe). Depression may cause fatigue and/or lack of motivation for physical activity. Ten of our participants were on medication for depression.

Physiological and psychological factors may have contributed to the baseline MEP being lower then the norm (11).

In the current study, gains in MEP in the PwMS were greater than those previously reported. See Table 34 for a presentation of number of subjects, training modality, duration, intensity, frequency, and percent change in MEP in previous studies examining respiratory muscle strength training in PwMS and the current study. Olgiati et al, (131) reported baseline MEP of 47.1± 18.6 cmH_20 and post training MEP of 70.1 ± 33.0 cmH_20, resulting in a greater than or equal to 31% increase. Mean difference was not reported. Smeltzer et al, (168) reported baseline MEP for all their subjects ranging from 29.6 to 81.8 cmH_20 (mean of 56.8 ±16.4 cmH_20), while MEP for the control and trained groups was 63.2 ± 18.9 and 53.6 ± 14.9 cmH_20, respectively. Post training the MEP for all subjects ranged from 41.8 to 107.3 cmH_20, with a mean of 69.3 ± 19.6 cmH_20. The trained group had a mean improvement of 19.4 ± 9.9 cmH_20, this being a 34% improvement. Wiens et al, (189) reported mean baseline and post training MEP of MS patients as 29.8 cm H_20 and 32.7 cmH_20 respectively. Their nine subjects had a total change of 26.0 cmH_20 and a mean change of 2.8 cmH_20 equal to a 9.7% improvement. Their control patients, patients without MS, mean baseline and post training MEP were 24.5 and 23.4 cmH_20, which was a mean loss of -0.75 cmH_20 that being equal to a 3.0% loss. Gosselink et al, (52) reported baseline MEP of 31± 21 and 24 ± 7 for trained and control subjects at base line. These investigators reported a change of 8 ± 14 cmH_20 in their trained group. This was a change of 30 ± 46% of the initial MEP, while the change in their control group was a minus 4 ± 26% of the initial. Klefbeck and Nedjad (83) using inspiratory training, reported median and range scores, in parenthesis, of 49 (range

of 39-58) % predicted and 39 (range of 22 - 99) % predicted prior to training in trained and control subjects, respectively. MEP increased to 68 (range of 47-79) % predicted and 38 (range of 20 - 99) % predicted in trained and controls following training, respectively. In the current study, baseline MEP was no different at 64.47 ± 3.82 cmH_20 to that reported by Smeltzer et al (168), but higher than other studies (131). In the current study the change in MEP following training was greater at 26.04 ± 4.82 cmH_20 compared to any of the previous studies examining muscle strength training in PwMS. The mean change in MEP expressed as the percent change following training, 38%, and 44%, for the Mi and Mo subjects, respectively, was greater compared to previous investigations. Intensity may have been a factor in the greater gains.

Intensity is one of the three principle components of an exercise prescription, the others being frequency and duration. Intensity is composed of the level of the load and the total number of repetitions. The resistive load was not provided in three of the previous studies examining EMST in individuals with MS (131, 168, 189). In the fourth study the training load was 60% of the baseline (52). In the one study using inspiratory muscle strength training (IMST) the initial intensity was submaximal starting at 40 to 60% of patient's PImax and at the end of the training session was not to be perceived as more than 17 (very hard) on the Borg 6-20 RPE scale (83). Frequency of training in the current study was comparable to two of the previous studies, as subjects trained five days per week once or twice per day (52, 131). Whereas in two of the other studies participants trained seven days, twice per day and three days, once per day (168, 189). IMST subjects trained every other day for 10 weeks for a total to 70 sessions (83). The total number of repetitions was less in our study as our subjects performed 4 sets of 6

Table 34. Current and pervious studies examining respiratory muscle strength training in Individuals with MS

Authors Date	Number of subjects	Mode of training	Intensity	Duration (weeks)	Frequency	Sets & Reps	Percent change with training
Olgiati et al, 1989	8	R I &/or E *	Not given	4	5d/wk twice daily	2 of 3 - 5 min	Δ 20 cmH_20 +31% I (s) Δ 23 cmH_20 +31% E (s)
Smeltzer et al, 1996	10	P-T E	Variable Per subject	12	7d/wk twice daily	3S of 15R	Δ19.4±9.9 cm H_20 34% E (s) .07% I (ns)
Wiens et al, 1998	9	Music therapy	NA	12	3d/wk once daily	30 min	Not given (ns)
Gosselink et al, 2000	9	P-T E	60%	12	Part of regular physical therapy	3S of 15R	Δ 9±9 cm H_20 (I) 39±41% (s) Δ 8 ±14 cm H_20 (E) 30±46% (ns)
Klefbeck & Nedjad 2003	7	P-T I	40 – 60% initial, not > 17 on 6-20 Borg Scale at end of training	10	Twice every other day	3S of 10 R	Δ 25 cm H_20 59% (s) (I) Δ 17cm H_20 36% (s) (E)
Current study	17	P-T E	40% 1st wk, 60% 2nd wk, 80% 3rd – 8th wk	8	5d/wk once daily	4S of 6R	MSc 26.04 cmH_20, 40.39% Mi 24cmH_20 38%, Mo 29cmH_20 44%

Mode: R: resistive, P-T: pressure threshold, I: inspiratory, E: expiratory; Frequency: d: day, wk: week; Sets & Reps: S: set, R: repetitions; *= whichever was <70% of predicted

once per day in comparison to 3 sets of 15 time per day in the studies by Smeltzer et al (168) and Gosselink et al (52). IMST subjects completed 3 sets of 10 per session (83). Olgiati et al, (131) had their subjects train in 2 daily sessions of 2 periods of 3 to 5 minutes interrupted by a short period (3 to 5 minutes) of rest. Greater gains occurred in our subjects performing at a higher load with less total repetitions, suggesting that

intensity may have greater influence then frequency or duration. Intensity is just one factor that effects the neural and muscular adaptations seen with strength training.

Expiratory muscles are skeletal muscles and respond in similar fashion to a strength training program as do other skeletal muscles. At initiation of a training program, that is the first to the third week, the noted gain in strength is largely neural. Neural adaptations occur due to changes in the motor command, descending drive, muscle activation, motor unit, and sensory feedback (30, 112). However, which neural adaptation(s) occurred is not identifiable as assessment of neural adaptation was not undertaken in this study.

Neural adaptation can also result from diminished muscle activity such as following disuse due to immobilization or reduced physical activity. Most of the PwMS in the current study were moderately active, therefore reduced physical activity was not an issue in the development of reduced MEP. Seven of the PwMS were involved in some form of physical activity e.g., swimming, yoga, Ti Chi, and/or gym workout. Five were employed in positions that required moderate to high level of walking throughout the workday.

Muscle adaptation to training is characteristic to the specific type, i.e., resistive or endurance. Respiratory muscle strength improves following resistive training (99, 129). The amount of gain in strength is dependent on the specificity, duration, and intensity of the training (129). Gosselink et al (52), used a training intensity of 60% of MEP. Klefbeck and Nedjad (83) used a training intensity of 60% of MIP. Whereas, in the current study, the training intensity was 80% of MEP for the last six weeks of training. Higher intensity required greater generation of force to maintain the resistive value in an

opened position to permit exhalation. However the other studies examining respiratory training in PwMS did not report the level of resistance (131, 168) or did not use a mechanical device to train the respiratory muscles (189). Previous studies examining respiratory muscle strength training in other patient populations have used resistive loads ranging from 10% to 65% (90).

The training tool, a pressure-threshold device, necessitates that the load on the device must be achieved and maintained to allow expiration through the device. Sapienza et al (154) reported 47% and 48% increase in MEP in female and male high school band players following 2 weeks of expiratory muscle. Gains in MEP may occur through the use of brass or wind instruments without additional expiratory muscle training. Trumpet players who blow against the high resistance of the instrument in which they primarily using their expiratory muscles, had statistically greater respiratory pressures compared to normal controls (36). In contrast, expiration against a load has been reported not to result in greater MEP. Schorr-Lesnick et al (157) found no significant difference in peak expiratory pressures between singers and wind-instrument players in comparison to normal control subjects. As noted breathing against a resistance for either inspiration and/or expiration does and does not increase respiratory muscle strength as measured by maximal respiratory pressures. What is the response of the respiratory muscle to training – that is, what adaptations or lack of adaptations result in respiratory muscle from strength training?

The initial adaptations that were described above typically occur because of neural changes and over time there are muscular and biochemical changes (122-124). These changes are known to return toward baseline after the training stimulus is removed

with the time frame to return varying between 2 to 4 weeks (57, 135). Investigators conclude that the positive benefits of resistance training on the musculoskeletal system are reversed when training is withdrawn. Therefore, continued training, perhaps at a reduced frequency and intensity, is required to maintain the musculoskeletal benefit from exercise (191). Two of the studies examining respiratory muscle strength training in PwMS had a detraining component to examine changes after the training had stopped (52). Gosselink and colleagues, (52) re-examining MEP, MIP, FVC, and IPD three months after training was finished, reported MEP returned towards baseline level. The MEP of the PwMS in the current study was reduced at detraining compared to posttraining, but remained higher than at baseline. Baker (5) reported that expiratory muscle strength was maintained following 8 weeks of detraining in healthy subjects who had completed either 4 or 8 weeks of EMST. A longer detraining period may be necessary to ascertain the time frame for a significant loss of strength if the training is not maintained.

MIP

At each assessment the mean MIP of the PwMS compared to norms was less than predicted for age and gender (59). Our subjects with MS had a gain of 5.1 cm H_2O, this was an 8% improvement from pretraining to posttraining which was statistically significant. A further increase of 2.5 cmH_2O occurred from posttraining to detraining, which was not statistically significant. Comparison of the change in MIP in our subjects with MS with Olgiati et al, (131) is difficult as the training for each subject varied dependent on respiratory muscle strength. That is in the Olgiati study subjects received IMST and/or EMST if their respiratory muscle strength was <70% of predicted (131).

These investigators reported an increase of 19.7 cmH_2O, that being a change greater than or equal to 31% improvement over baseline MIP. Gosselink et al, (52) reported a significant gain in MIP (Δ -9 ± 9 cm H_2O, $p < 0.05$; this being a 39 ± 41%) compared to baseline, but not compared to their control subjects ($p = 0.06$) though their subjects were trained for MEP. These investigators suggested that the gains in MIP may have been due to an improved length-tension for the inspiratory muscles secondary to training reducing the expiratory lung volume (52). These investigators further suggested that in the presence of increased lung volume there was greater elastic recoil pressure to overcome the expiratory pressure. Unfortunately, as in the current study, measurements of total lung capacity and residual volume were not made. Other investigators have reported no gains (168, 189). Klefbeck and Nedjad (83), reported the median for change in MIP and MEP following 10 weeks of IMST. The MIP increased 25 cm H_2O, this being greater than or equal to 50% improvement, whereas the MEP increased 17 cm H_2O, this being greater than or equal to 36%. The baseline MIP and MEP of their subjects was lower than that of our subjects (53 ±30 and 54 ± 31 cm H_2O vs 60.31± 23.02 and 64.47± 15.75 cm H_2O, respectively). The decreased baseline MIP and MEP of the previous studies may be explained by the higher level of disability in PwMS in the previous studies. Though the baseline MIP was higher in the current study the gains in MIP following expiratory muscle strength training were less than previously reported (52), but greater than others (168, 189). In the current study the significant gains from pretraining to posttraining may have occurred as the subjects had to inhale to near total lung capacity to exhale against the resistance. As stated above there may have been a positive effect on

the length tension relationship of the inspiratory muscles. However no information is available to explain the continued non-significant rise in MIP from posttraining to detraining. One can speculate that the subjects continued to exhale fully prior to inhaling similar to the breathing pattern used during training. However, this does not seem logical as most individuals would resume their usual breathing pattern.

Detraining is the loss of gains following the removal of the stimulus. The MIP at detraining continued to be significantly greater than at pretraining, but not different from posttraining. In contrast Gosselink et al, (52) studying EMST in PwMS reported that the improvements in MIP tended to be higher, but failed to reach statistical significance after three months of detraining. Whereas Klefbeck and Nedjad (83), examining IMST in PwMS reported that in 4 subjects who continued to train for 4 weeks after the experimental training period of 10 weeks was completed showed continued improvements, but the improvements were not maintained in three subjects who periodically trained. Romer and McConnell (147), examining IMST in healthy subjects who trained for nine weeks, reported that their subjects who detrained for 18 weeks had a reduction in inspiratory muscle function at nine weeks. These investigators reported that the inspiratory muscle function of their subjects plateaued between nine and eighteen weeks, remaining above baseline values. In agreement with Klefbeck and Nedjad (83), subjects in the study by Romer and McConnell who participated in a maintenance program training at one-third of the frequency of their previous level were able to retain their inspiratory muscle function. Mujika and Padilla (125) noted that force production declines slowly, while strength performance of limb muscular may be maintained for up to 4 weeks of inactivity. However velocity dependent strength, that is isokinetic strength,

may decline significantly. The assessment of inspiratory and expiratory muscle strength is velocity dependent as subjects are encouraged to inhale or exhale as forcefully and as quickly as possible. Further study is needed to examine effect of detraining on respiratory musculature.

Pulmonary Function Tests

PwMS pulmonary function may be normal or reduced in the presence of reduced respiratory muscle strength (15, 177). The lung volumes and capacities (i.e., FVC, FEV_1, FEV_1/ FVC, and PEF, measured at each assessment) of our subjects with MS were less than predicted for age and gender (59). FVC examined as actual data and as percent of predicted was significantly less than our healthy controls, with the mean FVC of the PwMS being 84% of that of the healthy controls. FEV_1 examined as a percent of predicted was significantly different from our healthy controls with the mean for the PwMS being 85% of that of the healthy controls, while the actual data did not show a significant difference. Neither FVC nor FEV1 as actual data or as percent of predicted were found to have time differences compared to the healthy controls. EMST did not improve either the FVC or the FEV_1. PEF of the PwMS analyzed as the actual data was 78% of that of the healthy controls, but when analyzed as percent of predicted was 76% of that of the healthy controls. Examining PEF, as the actual data and as the percent of predicted, found a significant gain of 8.5% from pretraining to posttraining which remained significant being 5.7% greater at detraining compared to baseline.

Previous studies examining respiratory muscle strength training in PwMS have reported non-significant change or no change in pulmonary function. Gosselink et al (51) examining EMST in PwMS reported non-significant changes of 25 ± 63% of initial

following 3 months of training and 21 ± 57% of initial following 3 months of detraining. Olgiati et al, (131) examining IMST and/or EMST in PwMS reported a 21% increase in maximal voluntary ventilation (MVV), but no changes in static lung volumes following 4 weeks of training. Though no gains occurred in FVC and FEV_1 the investigators reported that "most of the participants felt strengthened subjectively" (131). Klefbeck and Nedjad (83) examining IMST in PwMS reported there were no changes in pulmonary function following 10 weeks of training. Additionally they reported that there was no improvement in subjective perception of physical endurance after morning ADLs In agreement with Olgiati and associates (131), but in contrast to Klefbeck and Nedjad (83) our subjects reported they felt they had more energy after training. The gains in PEF and the PwMS subjective perceptions following EMST in the current study may have occurred as the subjects in this study were less disabled due to MS then the previous studies.

Method of measurement of the pulmonary function or the level of neuropathology may result in differences in reported values. PEF of both our healthy subjects and PwMS was less than the peak flow of normal subjects in a study by Suárez and associates (175). These investigators, examining peak flow in normal and amyotrophic lateral sclerosis (ALS) participants, reported maximal peak flow of 8.2 ± 1.2 and 3.0 ± 2.4L/s for the normal and ALS participants, respectively. The PEF of our healthy subjects was less than that of the healthy subjects in the study by Suárez and associates (175). Whereas the PEF of our PwMS was greater than the that of the patients with ALS in the by Suárez and associates (175). Additionally, the PEF our subjects was comparable to or greater than other PwMS who had not participated in respiratory muscle training (170), as well as

those who had participated in respiratory muscle training (52). Smeltzer and colleagues (170), examining the reliability of the IPD in PwMS having a median EDSS of 7 (range from 2 to 9), but not a training study, reported a mean PEF of 5.2 L/s which is comparable to that of our subjects at pretraining (5.3 L/s) but less than at posttraining (6.01 L/s) and detraining (5.9L/s). Benefit of EMST and/or IMST on pulmonary function may depend on when it is initiated, that is the level of neural involvement of the respiratory system.

Strength and/or endurance gains achieved through training require adequate neuromuscular integrity. A conclusion in several of the studies examining respiratory muscle strength training in individuals with MS has been to start the training early in the disease process (52, 83, 189). The current study did recruit participants with minimal to moderate disability, presumably having less neuromuscular involvement. However the lack of change in pulmonary function in PwMS at lower level of disability is similar to those at higher level of disability. Explanations as to the lack of increase in FVC and FEV_1 in the presence of increased MEP are limited. First, lack of increased in FVC and FEV_1 may have occurred as it is known that above a certain transpulmonary pressure at a given volume, flow does not increase with driving pressure (45, 74). It is not the effort or MEP, but elastic recoil of the lung, which determines the maximal expiratory flows (74). Dayman and Mead and associates, as cited by Hyatt (74), identified and reemphasized the importance of lung recoil in setting maximal flow, respectively. The lung recoil is determined by lung volume and properties of lung tissue. At a given volume there is a maximal flow that is a limit to expiratory flow independent of driving pressure. Secondly, the intrinsic state of the lung may also influence expiratory flow. If a change

in the lung tissue occurs over time due to the disease process of MS than strengthening the muscles of respiration would not influence the pulmonary function, however no literature was found that supports this concept.

Changes in pulmonary function in response to respiratory muscle strengthening have produced conflicting results and may be dependent on the subject population receiving the training. Wang et al, (183) examining resistive inspiratory muscle training in individuals with chronic cervical injury reported a non-significant increase of 14.3% of initial PEF following 6 weeks of training while MIP significantly increased 12.5% of initial and MVV increased 17.1% of initial. Biering-Sorensen et al, (9) examining respiratory muscle strength training in patients with complete tetraplegia who trained for 6 weeks using a fixed expiratory resistance and an increasing inspiratory resistance set by the patient, reported a significant increase in PEF but no change in lung volumes. Liaw et al, (101) examining resistive inspiratory muscle training in patients with complete tetraplegia who trained for 6 weeks reported a significant increase in FEV1 % of predicted and MVV as well as TLC, TLC% of predicted, and vital capacity. Weiner et al (186), reported significant gains in FEV_1 and FVC values in patients with moderate to severe myasthenia gravis following inspiratory muscle training. Playing wind or brass instruments provides a resistive load to expiration similar to the pressure-threshold device. Players of such instruments showed no difference in pulmonary function compared to non-players. Fiz et al (36) reported no statistical difference in pulmonary function in individuals who had played trumpet for at least 4 years and non-trumpet players. Schorr-Lesnick et al (157) reported no difference in pulmonary function between singers and wind-instrument players in comparison to normal control subjects. Strength

gains in expiratory muscles by means other than resistive load have resulted in similar findings. Training designed to increase abdominal strength achieved significant increase in strength, but no change in occurred in FVC and FEV_1 (165). Use of an anticholinesterase agent, e.g., Tensilon in patients with MG resulted in increased MIP and MEP but no change in pulmonary function (120).

Limited data exists as to the effect of detraining on pulmonary function. The mean PEF of the PwMS was significant different at detraining from that at pretraining, although there had been a reduction from posttraining to detraining. Gosselink et al (51) reported a return toward baseline and no statistical difference between 3 months following the end of training, i.e., detraining period of three months, compared to initial. Further study may be warranted to examine the effect of detraining following respiratory muscle strength training on pulmonary function in patient populations and healthy subjects.

Airway resistance

Resistance of any system is the relationship between the driving pressure and the resultant flow produced by that pressure. Total respiratory resistance is made up of the chest wall, lung tissue, and airway components (16). The resistance of the respiratory system can be partitioned into the upper airway resistance which includes the nose, larynx, pharynx, and trachea and a lower airway resistance which includes the bronchi and small airways (33). Fry (45) noted that upper airway resistance, that toward the mouth beyond the flow limiting point had little effect on maximal flow. In impulse oscillometry, the method used to measure airway resistance in the current study, the nasal passages are occluded. Therefore in impulse oscillometry it is the resistance of the lower

airways that had the largest impact on total airway resistance. The resistance of the lower airways is defined as recoil pressure, within the alveoli, divided by maximal flow. The major resistance to flow in the lower airway is between to lobar bronchi and the luminal on the respiratory bronchioles (16).

Resistance of the airways was assessed through impulse oscillation (IO), also known as forced oscillation (FO). In the IO technique the lungs are connected to a loudspeaker, which is powered by a sine wave generator and driven at a frequency of about 4-5 cycles per sec (72). IO reduces the elastic component of changes in pressure to a negligible amount. As the breathing patterned used in IO is a quiet, non-effortful breathing the inertial component of pressure drop is negligible. Therefore the pressure drop across the system is due to the resistive component. The respiratory resistance is determined from the relationship between the flow measure by a pneumotachograph and pressure measured by a transducer at the lips.

Abnormalities of tissue resistance in the usual frequency range (4 to 40 Hz) of IO have not been reported (133). Airway obstruction is considered when there is an increase in respiratory system resistance (Rrs). Systemic change in the distribution of flow is suggested by a negative frequency dependence of Rrs. The change in frequency may be due to peripheral or central airway obstruction (133). Subjects in this study had frequencies within the normal range (11.9 to 13.2 for H and 12.2 to 15.0 for the MSc groups). However, what was unusual was that the resonance frequency of the H group decreased with training continued at a lower level at the detraining assessment. In comparison the MSc group increased with training and continued to increase, having a higher mean resonance frequency at detraining. No literature exists which examines the

effect of respiratory muscle training on frequency. A possible explanation of the increased frequency at posttraining and detraining is that several of the MSc were having either upper respiratory infections or sinus – allergy irritation at the time of retesting. Due to the travel time and distance for most of the MS subjects, the subjects could not be requested to return at a later date for retesting.

Though resonance frequency was the only component of airway resistance that was significant, the Rrs of our subjects was found to be greater than previously reported data (16, 29, 92, 133). Rrs of the PwMS group increased from 4.2 to 4.5 to 4.9 cmH_2O /l/s from pretraining to posttraining to detraining, respectively. Whereas, the H group had identical amount of decrease from pretraining to posttraining (4.3 to 4.1 cmH_2O), as increase from post to detraining (4.1 to 4.3 cmH_2O).

Rrs has been predicted for healthy subjects and patient populations using the body plethysmograph and IO. Peslin (133) citing previously reported data obtained from subjects in a body plethysmograph, noted that Rrs was 1.85 ± 0.622 with a maximum of 2.86 cm H_2O for males and 2.029 ± 0.602 with a maximum of 3.02 cm H_2O for females. Dubois et al, (29) as cited in Campbell et al, (16) reported similar total respiratory resistance of approximately 1.6 – 2.5 cmH_2O. Peslin (133) citing previously reported data obtained from subjects using FO, noted that Rrs was 2.55 ± 0.612 for males and 3.11 ± 0.612 for females. Làndsér and colleagues (92), whose subjects were not separated as to gender, but level of smoking (non-smoking, light smokers, and heavy smokers) reported the mean Rrs was 2.55 ± 0.612 in non-smokers. In contrast to these investigators the Rrs in the current study for males and females was slightly higher, 3.95 and 4.47, respectively. There was no statistical difference in Rrs between the H (mean of 4.2,

ranging from 2.5 to 10.3) and the MSc (mean of 4.53, ranging from 2.3 to 9.7) group. Examination of the data of the male and female subjects and that of the MSc and H groups revealed an unusual pattern. From pretraining to posttraining there was a non-statistical reduction in the Rrs of the male subjects and the H group compared to the female subjects and the MSc group, respectively. Whereas the male subjects and the H group returned toward pretraining values at the detraining assessment, the female subjects and the MSc group continued to increase in Rrs from posttraining to detraining. This pattern is partially explainable in that the majority of MS subjects were females. However, is it the gender or the disease that precipitated the increase in Rrs? Also, as discussed above several of the individuals with MS had respiratory inflammation at their posttraining and detraining evaluations. The inflammation may have increased the resistance of the lower airways.

Limited data exists as to the effect of MS on respiratory resistance. Buyse et al (15) examining respiratory function in patients with MS reported total airway resistance 2.75 ± 1.43 cm H_2O $l^{-1}s$, this being $121 \pm 68\%$ of predicted. However, comparison of these data to that of the current study may be limited as 15 were ex-smokers and 20 current smokers. Eleven of their subjects had an obstructive respiratory pattern, 13 a restrictive pattern, and 8 a mixed pattern. The subjects underlying respiratory disorder may have influenced the airway resistance. Data does exists as to the effect of gender on Rrs. White and associates (187) examining pharyngeal resistance in normal subjects, reported that men had higher pharyngeal and supraglottic resistance than women. Jiemsripong and associates (78) examining Rrs in healthy subjects, aged 21 to 64, reported a mean of 2.5 ± 0.62 with the Rrs being greater in females than males. Rrs has

been found to be greater in females than in males by several other groups of investigators (35, 42, 173). Peslin and associates (134) reported the Rrs, measured at 10 Hz, was greater in women than in men. Additionally, these investigators reported that the expiratory resistance was slightly larger than the inspiratory resistance (134). In the current study, resistance was not examined as to inspiratory and expiratory resistance, however that would be of interest in future studies as patients' with MS have been noted to have resistive and / or obstructive lung disease. Determining which component of airway resistance is more impaired may lead to potential treatment.

Assessment of Rrs by techniques other than IO have resulted in somewhat different values. Baydur and Carlson (7), using the passive relaxation technique to measure Rrs, reported mean values of 9.26, 8.26, and 8.07 cm $H_2O \cdot l^{-1} \cdot s$ in neuromuscular, sarcoidosis, and control subjects, respectively, this being almost 4 times greater than the other noted investigators and 2 times greater than that in the current study. State of one's health does appear to have an effect on airway resistance. However, at this time limited data exists as to the effect of specific diseases, particularly neurological or neuromuscular, on Rrs.

Previous investigators have partitioned resistance as to location within the respiratory system. The glottis-larynx and the mouth accounted for twenty-eight percent of the total resistance (16). Peslin and associates (134) suggested that the glottic aperture was a major factor in the flow dependence of Rrs. Additionally, these investigators suggested that the volume dependence of Rrs implicates the phasic opening and closing of the glottis. No MS participants were found to have abnormal vocal cords on physical inspection by endoscopic examination. The slightly higher than normal total resistance in

participants may have occurred in the lower airways as the mean peripheral airway resistance component of impedance [Rp] was 3.0 cmH_2O /l/s pre- and post- training, and increasing to 3.2 cmH_2O /l/s at detraining. Whereas, the central airway resistance component of impedance [Rz] increased from 2.2 to 2.6 to 2.7 cmH_2O /l/s from pre- to post- to detraining, respectively. The Rz increased 0.5 cmH_2O /l/s in the PwMS from pretraining through to detraining, while there was an overall decrease of 0.1 cmH_2O /l/s in the H participants. The slight gain in impedance in the PwMS may have resulted from a change in the tone of the smooth muscle of the airway system as autonomic nervous system dysfunction occurs in PwMS. Increased tone of the smooth muscle may cause increased circumferential and longitudinal tension, causing the larger airways to become less compressible. Therefore, the slight change in impedance may have been due to change of tone of the smooth muscle of the medium sized bronchioles. MS plaque locations may affect airway resistance if a plaque is found along the path of the vagus nerve, which is responsible for maintaining normal bronchial muscle tone (16).

Maximal Voluntary Cough

This is the first study to present measured data on maximal voluntary cough in PwMS. Previous investigators have reported impaired cough in PwMS using the IPD, a questionnaire composed of subjective and limited objective measurement (52, 168). Prior to this study no data was available on the effect of EMST on cough in PwMS or a normal population.

Cough Volume

Cough volume was less at all measurements in the PwMS compared to the healthy controls. Healthy participants' mean volume (2.2 ± 0.12 L) was identical to

previously reported mean of volume 2.2 ± 0.46L (103). The mean volume of the PwMS participants, 1.67 ± 0.12L, was slightly below normal, but greater then that for patients with airway obstruction, 0.66 ± 0.22L (103). During each assessment the mean cough volume for the healthy participants was equal to normal values, and therefore would not have been expected to increase even in the presence of increased MEP. PwMS began with a mean cough volume below normal and no significant change was found at the posttraining and detraining assessments. As indicated above, cough volume is dependent on the level of lung volume at which one initiates the cough, this being influenced by the amount of inspired air. Reduced inspiratory time or weakened inspiratory muscles could limit the amount of air inspired. PwMS may have abbreviated time of inspiration (60). PwMS having less than normal inspiratory strength at each assessment may have brought in an amount less than TLC even though they were encourage to fill their lungs completely. However, lung volumes other than those examined by spirometry were not assessed during this study. Therefore, it was not possible to determine if these subjects were beginning their cough at levels lower than TLC. Another possibility for the lack of improvement of cough volume may be change in the collapsibility of the airways due to change in the tone of the airway smooth muscle, innervated by the parasympathetic division of the autonomic nervous system. Neural control of the smooth muscle is the autonomic nervous system, which is reported to be effected by MS (37). Extensive body of literature exists reporting autonomic nervous system dysfunction in PwMS (37, 49, 55). However, during this study the state of the autonomic nervous system was not assessed.

Cough Air Flow

PwMS had significantly different values for all cough variables except for flow and its derivative, peak amplitude, in comparison to H participants. Flow and peak amplitude were generally one to one and a half liters less in the PwMS compared to the H subjects. Both groups, whose peak cough flow (PCF) ranging from 6.2 ± 0.21 to 7.4 ± 0.18 L/s, were slightly higher than previously reported values for patients having received a laryngectomy (5.42 ± 0.19) and healthy controls (5.86 ± 0.72) (39). Hammond et al (172) examining cough in individuals who had sustained a stroke, reported cough peak flow in normal subjects as 1.8841 ± 0.226 l/s and the patients as 0.8751± 0.1227 l/s, these being substantially different than that reported by Fontana et al (39) and in our subjects. However, both our PwMS and H group had lower PCF than that noted by Suárez and associates (175), who reported mean PCF of 11.58 ± 1.16 for normal subjects in comparison to and 3.55 ± 3.22 L/s for ALS participants. The difference of PCF and PEF as a percent of PEF ([PCF-PEF/PEF] x 100) has been proposed as a measure to monitor the change in expiratory muscle weakness in patients with neuromuscular disease. Suárez and associates (175), reported this difference in healthy participants and patients with ALS as being 43 ± 13% and 11 ± 17%, respectively. In contrast the H group in our study had much closer values than our PwMS: H group at pretraining -2.80%, posttraining -2.53%, and detraining -3.02% as the PCF was less than the PEF, but both being normal range. The values for our PwMS ranged from less than to comparable to higher than their ALS participants, dependent on assessment and level of disability: Mi group at pretraining 30.27%, posttraining 13.60%, and detraining 14.75%; and Mo group at pretraining 4.70%, posttraining 2.23%, and detraining 13.58%. Suárez and colleagues,

(175) reporting the ratio, ([PCF-PEF/PEF] x 100), values for two subjects over a 24 month period suggested that a diminishing percent of PEF, indicated increased weakness of the expiratory and/or laryngeal muscles. Measurements in this study do not agree with this as there was a decrease in the ratio in the Mi and Mo groups from pretraining to posttraining while our subjects increased their MEP over the same time period. Further investigation into the use of this ratio, ([PCF-PEF/PEF] x 100), is warranted to clarify its used as a clinical tool to monitor MEP in patients with neuromuscular as well as neurology disease.

Flow rates during the explosive phase of cough have been reported to be as high as 10 to 12 L/s (96-98) this again being substantially different from the mean PCF achieved by patients or H subjects in the current study. However, two participants of the study had similar flows, i.e., $\geq$ 10 L/s, which increased one to three liters more with training. The PCF of these two participants is similar to the PCF for healthy controls (11.58 $\pm$1.16 l/s) in comparison to patients with ALS (3.55 $\pm$ 3.21l/s) (175). The volume within the lung has an important bearing on PCF.

Peak cough flow is normally measured following a deep inspiration. Cough begun at high lung volume improves the mechanical function of the expiratory muscles due to optimized length-tension relationship. Kang and associates reported increased PCF in patients with neuromuscular disease following increased maximal insufflation to near predicted VC levels (79). In the current study subjects were instructed to inhale as deep as possible before coughing. Coughs that sounded weaker or looked substantially different were repeated to obtain ten acceptable coughs. The amount of air inhaled in the initial phase of cough, that is the inspiratory phase, influences the peak cough flow as

well as the cough volume. Leith, (97) examining previously reported data on cough, reported that the cited data showed that the combined volume of three coughs was 85% of FVC, therefore they achieved their cough close to 90% of TLC. Whereas coughs begun at lower lung volumes result in reduce expiratory phase volume such as those begun close to FRC in male and female subjects beginning achieving 1.1L and 0.6 L, respectively (97). Cough volume would be reduced if participants coughed at various levels of lung capacity, therefore participants were encouraged to inhale as deeply as possible to achieve TLC prior to cough.

Rise Time

Peak cough flow rise time (T_R), the time from the end of the compression phase to the peak of flow, was significantly slower at each assessment in the PwMS compared to the H group. Rise time of our H participants was comparable to reported T_R values for healthy controls which has ranged from 0.0295 to 0.05 second (40, 172). The T_R of the H participants increased non-significantly, becoming faster, from pretraining to posttraining, followed by a slowing in T_R at detraining. Gains in MEP could explain the faster T_R. However, in the presence of significant improvement in MEP in our PwMS, their T_R continued to be slower than H values from pretraining through detraining, (i.e., $0.064 > 0.071 > 0.084$). These values are comparable to the T_R of patients who have sustained laryngectomy or stroke ranged from 0.055 to 0.15 sec, respectively (40, 172). Within the H group the pattern of improvement then loss follows that of expiratory strength muscle. Initial gains in strength are known to be neural, which includes better muscle coordination. Gains in T_R may have occurred secondary improved neural activation of the muscles. In contrast, T_R in the PwMS decreased, i.e., slowed from

pretraining through detraining. In the presence of increasing MEP the loss of T_R is difficult but may again have to due with coordination of the muscle activity, which may be slower in PwMS due to decreased neural conduction.

Cough Volume Acceleration

Cough volume acceleration (CVA), the ratio of the peak flow over rise time [flow (l/s)/T_R (s) = CVA l/s*s^{-1}) has been used as a measure of cough intensity (40, 172). Earlier, Fontana, et al (39), proposed using the ratio of the peak of the integrated electromyographic signal over the time to the peak of the signal as a measurement of cough intensity. As yet, only two studies have used CVA as a measure of cough intensity. Fontana et al (40), reported a mean CVA of 199.25 ± 28.06 CVA l/s*s^{-1} for non-patient controls. Mean CVA of our subjects at pretraining was just slightly greater, 212.89 ± 35.36 CVA l/s*s^{-1}. Following EMST the mean CVA increased 15%, achieving 244.67±35.27 CVA l/s*s^{-1}, however not reaching statistical significance. PwMS began with a mean CVA of 128.91±19.86 CVA l/s*s^{-1}, which increased 7.75% to achieve 138.22 ± 28.58 CVA l/s*s^{-1}, however it did not reach statistical significance following training. The mean CVA of our PwMS was higher than that achieved in patients who had undergone a laryngectomy who had a mean CVA of 92.32 ± 10.62 CVA l/s*s^{-1} (40). Mean CVA of our subjects, both H and PwMS were substantially greater than those reported by Smith-Hammond et al (172) for patients who had sustained a stroke and control subjects.

Leading Slope

The leading slope is the slope of the line that connects the lower and upper threshold points on the waveform. This is the mathematical equivalent to an 'average

slope'. The leading slope of the PwMS was found to be significantly slower than that of the Healthy group. No difference in leading slope was found when the MS data was separated as to level of disability. In the study by Fontana they set their lower threshold at 10% above the baseline. In the current study the lower threshold was set at the baseline to catch the moment the expiratory phase begun. That may explain the difference in rise time, as discussed above. No literature exists that discussed the leading slope of a cough wave form in healthy or patient populations.

Index of Pulmonary Dysfunction

The IPD was developed as a clinical tool to assess the pulmonary status of individuals with MS in a non-invasive manner (170). It is both a subjective and objective assessment of respiratory status. Of the four tasks three are subjective and one is objective, i.e., counting out loud for as long as possible following a deep inhalation. PwMS were not able to count for as long as the healthy controls, raising their score. The IPD is a good quick check of the respiratory status of PwMS.

Limited data exists on the use of the IPD in PwMS (52, 169, 170). Our pretraining results are comparable to Smeltzer and associates (170) who reported 19 of forty subjects (47.5%) having low score (4 to 5), 16 of forty (40.0%) having moderate score (6 to 7) and 5 of forty (12.5%) having high score (9 to 11). In the current study, at pretraining 8 of seventeen (47.0%) had a low score, 8 subjects had a moderate score, and one subject had a high score. Smeltzer and associates (169) reported their subjects' mean MEP as 51± 22 which was lower than that of our MS subjects who had mean MEP of 71.6 ± 10.9. Limited data exists as to the change in the IPD following training.

IPD has been reported in only one other study examining EMST in individuals with MS (52). IPD, which ranged from 8 to 11 with a mean of 10 improved such the range was 6 to 11, however the mean continued to be 10 (52). In the present study the pretraining IPD mean for the PwMS was 5.8 with a range of 4 to 9, while the posttraining IPD mean was 5.6 with a range of 4 to 8. Following training two of our subjects improved such that their scores decreased from moderate to low score. Following detraining these two participants' IPD scores returned to moderate. However an unexpected finding occurred in that the PwMS with the high score at pretraining and posttraining achieved a moderate score at detraining. The participant's MEP had increased 100% from pretraining to posttraining, but had decreased 10% from posttraining to detraining. This suggests that change in IPD score is not only influenced by change in respiratory muscle strength, but others factors as well. The use of the IPD as a clinical tool may be limited as it gives an overview to the respiratory status function, but does not look specifically at the respiratory muscle strength. Future studies are needed to determine the reliability and validity of this tool for assessment of pulmonary function in PwMS over a period of time.

Detraining of Cough

Effects of detraining of on cough has been examined on a very limited basis. As described Gosselink et al (51) reported that the improvement on cough in PwMS, as assessed by the IPD, remained significantly better in their training group three months after training was stopped. Baker (5) reported that compression phase time was significantly different at the end of the fourth week and the eighth week of the detraining period, though there was no difference between the compression phase time at baseline

and after eight weeks of training. In the no current study cough measurements were found to have significant time effects therefore no difference was found between any of the assessment period indicating that detraining did not influence cough.

Cough: a ballistic action?

Lack of improvement of the maximal voluntary cough may have occurred due to lack of specificity of training. Training specificity is important. Recommended principles of training for skeletal muscular suggests that a change in muscle structure, such as achieved through weight training, should be accomplished prior to the commencement of specific explosive power training (84). A non-invasive method to determine a change in the abdominal muscles structure would be to continue pressure-threshold training until there was no further increase in MEP. Cough may be considered a ballistic action as it involves an explosive phase.

Ballistic, in the Merriam-Webster dictionary, is defined as of or relating to ballistics or to a body in motion according to the laws of ballistics. Ballistics is defined as the science of the motion of projectiles in flight and also as the flight characteristics of a projectile. Ballistic action / skill involves a stretch-shortening cycle. Most power activities involve a counter movement during which the muscles involved are first stretched rapidly and then shortened to accelerate the body or limb (84). Stretching an activated muscle prior to its shortening enhances its performance during the concentric phase. The velocity during and the force achieved at the end of the eccentric (pre-stretch) enhances the average concentric force and average mechanical power (13). In a cough during inspiration to TLC the thoracic and abdominal walls move outward increasing the anterior-posterior circumference. This provides a stretch to the abdominal muscles prior

to shortening during the explosive phase of cough. A cough involves high velocity force to expel mucus or a foreign object. Pre-stretch speed and short coupling time are associated with enhanced performance during the concentric phase (13). Pressure-threshold training preformed in a manner to increase the pre-stretch speed and shorten the compression time then perhaps the concentric (explosive phase of cough) would be enhanced. Kraemer and Newton (84) reported that light load, explosive training is the best method of training to achieved high velocity force production. Recommended intensity for light load, explosive training is 30% of 1 repetition maximum (RM). Future study should examine the use of the pressure-threshold trainer at a lower training intensity, i.e., 30% of 1 RM preformed in an explosive manner, similar to the activity that occurs during the exhalation phase of cough.

Speech

No study has examined the effect of respiratory (inspiratory and/or expiratory) muscle strength training on speech performance in individuals with MS. Data exists as to the perceptual changes of speech in PwMS (20, 26, 61-64). Most noted perceptual speech signs include impaired respiratory support for speech, deficits in pitch variation and pitch steadiness, abnormal prolongation of intervals during speech, and a harsh voice quality. Other deviations include disorders of phrase length, general pattern of stress, deficits in loudness variation, and imprecision of consonants (20, 26, 61-64). Additional deviations, particular to PwMS having cerebellar ataxia, occur in the areas of prosody and articulation (64).

Acoustic

Vowel prolongation

At each assessment PwMS prolonged the vowel /a/ for a shorter duration than H participants. PwMS group prolonged the vowel for a shorter period at each loudness level compared to the H group. Additionally, the length of vowel prolongation was significantly different at the N loudness level compared to L loudness level only in the H group and not in the PwMS.

No data exists as to the effect of EMST on the phonation capacity of PwMS. Wiens et al (189) examining EMST in PwMS used a singing protocol. These investigators described their training as "relaxation and diaphragmatic breathing, intonation of syllables, and reading or singing phrases, paragraphs, and simple songs". They further described their protocol as "diaphragmatic breathing exercises, which challenged the volume of breath intake and the rhythm of breathing". However, no data was presented on the effect of the protocol on ability to phonate either by speech or in singing at baseline or at completion of training. No explanation was given by the authors for the lack of outcome data on these variables. The current research was undertaken to examine the effect of EMST on phonation in PwMS and in comparison to healthy subjects receiving EMST.

Phonation is achieved by the flow of air around and over the vocal folds causing them to vibrate. The minimal amount of air pressure required to maintain vocal fold vibration is 2 cm H_20. However larger alveolar pressure, i.e., 15 to 20 cm H_20, is needed for L speech and singing (196). Speaking at low lung volume level requires the generation of high expiratory pressures. Therefore, gains in MEP for the PwMS and the

H subjects would be of benefit. Pretraining measurements showed a statistical difference in vowel prolongation between the PwMS and the H subjects. Each group had mean MEP, which was sufficient to produce L phonation at each of the three assessments. Prior to EMST the mean MEP of the PwMS and the H subjects were 3 to 3.5 times and 7 times greater than that needed for L phonation. Following EMST MEP increased to 4 to 4.5 times and 9 times greater than necessary for L phonation in PwMS and H subjects, respectively. These gains in MEP were weakly correlated to vowel prolongation, i.e., 22.3% and 20.3% for N and L intensity levels.

An increase in MEP should correspond to an increase in subglottal pressure (Psg) if the vocal folds are functioning properly. Visual screening of the vocal folds of PwMS were judged to be normal, however no stroboscopic assessment of the function of the vocal folds was available at the time of this writing. Normal closure of the vocal folds should have allowed an increase in thoracoabdominal pressure, i.e., subglottal pressure, to develop.

Subglottal pressure is produced by a combination of passive and active of the respiratory system. Gains in MEP were hypothesized to improve speech production as assessed by vowel prolongation at two phonation intensities. The increased MEP in PwMS and H subjects did not result in gains in vowel prolongation in the PwMS compared to the H subjects. However, within each group vowel prolongation increased from pretraining to posttraining and continued on to the detraining. Our data is in agreement with Ladefoged and McKinney (89) who reported that for words spoken at various loudnesses the Psg is proportional to the effective sound pressure. These investigators reported that an increase in Psg of about 6.5 cm H_20 was accompanied by

an increase in frequency of half an octave (89). Increased Psg may permit PwMS to speak with less stress at a higher frequency. Increased Psg may permit PwMS who are singers to reach the higher register on the music scale.

Perceptual assessment of speech deficits in PwMS have been studied since the late eighteen hundreds. The first recording of acoustic components was accomplished by Scripture (158). He reported the presence of irregular waves, which he attributed to laryngeal ataxia. Darley and associates (26) reported that impairment of loudness control was the most frequent deviation in their subjects. In agreement with Darley and associates (26), PwMS in our study were less able to generate phonation, i.e., vowel prolongation, compared to H group. Diminished vowel prolongation being was significantly different at the L loudness level. During vowel prolongation at an N level there was a 2 second difference between the PwMS compared to H group, whereas at the L level there was a 6 sec difference. Diminished Psg in the PwMS may have resulted in the shortened vowel prolongation in the PwMS.

No data exists as to the effect of removal of EMST stimulus on vowel prolongation ability PwMS and healthy subjects. PwMS and healthy participants increased the time period for vowel prolongation at each assessment such that at the detraining assessment vowel prolongation was significantly different, i.e., greater than at the pretraining assessment, though the training stimulus had been removed 4 weeks prior. Limited data exists as to detraining in speech therapy. However, investigator's reported that patients with Parkinson Disease were perceived to be 'louder' and their voice of 'better quality' at 12 months after the completion of training compared to prior to training using the Lee Silverman Voice Treatment (LSVT) which emphasizes high phonatory-

respiratory effort (139, 155). Investigator's reported that the patients maintained improvements at a 2 year follow-up after participating in LSVT (141). Is it the deeper breath, the high intensity, and/or better coordination between the oral motor muscular and muscles of expiration that permits increased phonation after the removal of the stimulus – further research is needed in healthy subjects and patient populations.

"My Grandfather" passage – words per minute

The standardized 'My Grandfather' passage is composed of 133 words (26). Reading the passage was used to determine the number of pauses / breath-breaks needed during connected speech. Scanning speech, typically associated with MS, produces speech in which the normal speech pattern is disrupted with abnormally long pauses between words or individual syllables of words. Only one other study has used this passage with PwMS (26). Comparison of the reading rate with was not possible as the investigators did not provide data on the reading rate (26). Reading rate has been reported by other investigators using another passage (62). Hartelius and colleagues, (62) using a reading task with 89 words, reported words per minute (WPM) ranging from 76 to 153 in three males with MS and from 98 to 172 in two females with MS. Unpublished speaking rate data for the same reading task, cited by Hartelius and colleagues, (62) reported a mean of 148 WPM with a range variation of 58 to 235 WPM. Hartelius et al, (62) compared their patient and normal subjects speech rate to published data which reported a normal speech rate in a paragraph-reading task is 160-170 (34). A normal male and female produced speaking rates of 190 and 160 WPM, which they compared to unpublished normal data of 177 WPM which ranged from 121 to 221 WPM (62). In comparison, the PwMS had a mean rate of 177 WPM (177 ± 3.14), while the H group

had a rate of 206 WPM (206 ± 2.42). The variation in range seen in our subjects is comparable to published data. Prior to training the variation in range for PwMS was 143 to 215 WPM, which increased by 3 to 13 WPM posttraining. Our H participants speaking rate was 172 to 235 WPM at pretraining, which increased by 3 to 11 WPM posttraining. A significant gender difference was found within the PwMS in which the females read faster than the men (172 verse 162 WPM). In comparison within the H participants the women had comparable reading speeds to men (206 to 208 WPM). The slower WPM in the PwMS may have resulted from a diminished respiratory support for speech which is one characteristic of the dysarthria that is seen in individuals with MS (63, 64). A second possible cause of slower reading time is visual acuity in the PwMS, which ranged from normal to moderately impaired. Visual acuity may change depending on temperate (increased temperate further impairs signs and symptoms), stress, or fatigue; or as several PwMS called it – "having a bad MS day" (27, 107).

Other noted characteristics of MS dysarthria are deficits in pitch variation and pitch steadiness, abnormal prolongation of intervals during speech (i.e., longer pauses), a harsh voice quality, disorders of phrase length, general pattern of stress, imprecision of consonants and deficits in loudness variation (63, 64). Deviations in respiratory support, phoneme length, defined as degree of speech sound prolongation, and phrase length, defined as adequacy of phrase length and expiratory air flow, occurring in greater than 50% of a MS subject population suggests the presence of reduced subglottal pressure and a reduction in expiratory pressure (63). Diminished respiratory support may be a factor in the long-term instability, characterized by variation in vocal frequency and intensity, as noted by Hartelius and associates (61). Intensity may be influenced by the generation of

adequate subglottal pressure. Can maintenance of intensity during a task be inferred from the performance of the task?

As with the vowel prolongation, the reading task was performed at N and L loudness. Though the PwMS had a lower WPM they maintained their reading rate at both loudness level (179 and 176 WPM, for N and L, respectively) compared to the healthy controls (213 and 199 WPM for N and L, respectively). Hartelius and colleagues (64) reported increased syllable duration and interstress interval duration in individuals with MS compared to normal controls when reading a nonsense passage in Swedish. Increased syllable duration and interstress intervals could lead to reduced WPM as seen in the current study. These investigators suggested that the increased syllable duration may have resulted from impairment at the *segmental* level (64). At this level the segment durations are influenced by the speaking rate, phonetic context, utterance position, stress, inherent characteristics, type of speech material, speaking style and speaker characteristics (64). The interstress duration occurs at the suprasegmental level. Stress groups, having one stressed and multiple unstressed syllables, do not occur at regular time intervals during lengthened interstress durations. In contrast to PwMS patients with Parkinson's disease (PD) having lower oral pressure compared to healthy subjects were found to have faster interpause speaking rate (174). Similar to the PwMS the patients with PD did produce fewer syllables and spoke for less time per breath than normal subjects (174). Therefore the cause of decreased WPM may be due to other factors than just decreased subglottal pressure. Lung volume, an important factor in subglottal pressure generation due to the length-tension influence on respiratory muscles has been reported to have a high degree of intrasubject and intersubject variability (190).

Lung volume variability may have been a factor in the limited differences seen with training. However, lung volumes were not monitored during the vocalization assessments. The decrease in WPM in the H group at N SPL compared to the L may also explained by change in lung volume which is known to influence speech intensity. Laryngeal and/or respiratory adjustments may be used to adapt speaking intensity levels (190).

No study could be found that has examined the reading rate, assessed as WPM in healthy controls or PwMS following a period of detraining. PwMS word per minute increased from pretraining to posttraining and on to detraining, while the WPM of the healthy group decreased from pretraining through to detraining. The reduction of WPM in the healthy subjects is an oddity. It can be speculated that at the pretraining assessment the reading of the passage was a novel task and the subjects were more intent on performing the skill while at the posttraining and detraining the subjects may have been reading more at their typical rate. Use of a metronome would cause targeting of the reading speed and therefore would give a false measurement of the WPM. Performance by the healthy subjects and the PwMS may have been influenced by a practice effect, which will need to be controlled for in future studies.

Aerodynamic

Normally when there is an increase in pressure the airflow also increases but the relationship of pressure to flow is dependent on the resistance to flow, the magnitude of the obstruction to the outgoing air. When the glottis is closed and the resistance remains the same, an increase in pressure will cause an increase in flow. However, in the presence of decreased resistance, that is an opened glottis, the flow will increase without an

increase in pressure. Aerodynamic examination of flow is normally discussed in relation to the components of open quotient, closed quotient, maximum flow declination rate and peak glottal airflow. However, due to calibration and recording issues pressure and flow data for the Papa passage and vowel prolongation were not available. The principle issue was the inability to get a clear calibration signal particularly for pressure, but also the flow signals. Additionally, the recording of several subjects had too much noise artifact that examination of the data was not possible. The relative pressure in millivolts for the repetition of 'pa' was the only data that could be analyzed. Data was limited due to pressure tube moving forward of the teeth which was not determined until off-line analysis showed spikes with a trough in between. An acceptable pressure recording would show pressure signals having a reasonably rounded top returning to zero during the stressed 'p' of the repeated 'pa'.

Increased MEP had been hypothesized to increase sound pressure level. An expected statistical difference was found between the N and L loudness. However, no statistical change in loudness at either the N or L were found following training. Though the PwMS had statistically lower MEP compared to the H participants no statistical difference was found for group on the repetition of 'pa' at the two loudness levels. Nevertheless, within this study two unusual events occurred: 1) at the L loudness no statistical change occurred in both the H and PwMS groups and 2) at the N loudness the H group had a significant decreased from pretraining through detraining, however no change was found in the PwMS. The decrease in relative pressure for N loudness of the H group may have occurred as the tubing in the oral cavity of several subjects slipped forward of their teeth, as discussed above. The decrease relative pressure found in H

participants with no change in relative pressure in PwMS may have occurred due to the technical problem in recording of this data.

No previous studies were found that have examined the aerodynamic components of speech in PwMS. Additionally, limited data exists as to the examination of aerodynamic components of speech in other patient populations or healthy subjects. Solomon and Hixon (174), examining the speech breathing in Parkinson's disease (PD), reported that oral pressure was statistically less in the patients with PD than in healthy control. In contrast, in the current study, there was no difference in pressure between the groups, but only between the intensity. Previous investigators have reported that with a doubling of the subglottal pressure an increase in loudness can be achieved (109). Jiang and associates (77) reported higher subglottal pressure was needed to achieve near normal flow rates in patients with Parkinson's disease compared to normal subjects. These investigators suggested that patient's with Parkinson's disease used greater subglottal pressure due to increased laryngeal resistance. This correlated with the patients' perception of having to work harder to produce phonation (77). This perception of having to work harder to speak was expressed by several of the PwMS in the current study. Most studies from the late 1990's until now have examined the use of a high intensity therapy, the Lee Silverman voice treatment (LSVT), in patients having Parkinson's disease. The program addresses the motor disorder, hypokinetic dysarthria, to improve the perceptual characteristics of voice. The treatment technique uses high phonatory effort tasks that stimulate increased vocal fold adduction and respiratory support. The goal is to increase amplitude of voice output, alleviate the effects of hypokinesia on the respiratory and phonatory systems of patients with Parkinson's

disease (161). Sharkawi and colleagues (161) reported statistical increase in vocal intensity and frequency and speech intelligibility. Dromey and associates (28) and Ramig and Dromey (140) reported that the increase in SPL following training with the LSVT was due to increased subglottal pressure, adduction of the vocal folds and rate at which the glottal airflow shuts off, that is the rate of adduction of the vocal folds, and its relation to vocal loudness (28, 153). Seeley (159), reported improvement on loudness, detectable by naïve listener, in six individuals with MS who had received the LSVT. However, two other perceptual characteristics, voice quality and intelligibility, did not improve sufficiently for the raters to determine a difference from before and following treatment. What is unique about this treatment is the intensity of the voice function. (159). The high-intensity (80% of MEP) produced a pressure possibility similar to the high intensity of voice function that occurs in the LSVT. However, the gains in MEP were not maintained while the gains following LSVT have been reported to be present as long as 12 months after training has been completed (28, 140).

Questionnaires

Dysarthria Scale

No study was found that has used this tool to examine the level of dysarthria in PwMS. Dysarthria, a motor speech disorder, is the most common communication problem observed in PwMS (8). Controversy continues to exist in the literature as to the occurrence of dysarthria in PwMS. Darley and associates (26) reported that 41% of their 168 patients presented significant speech deviations. Beukelman and associates (8), using a survey, noted that 23% of their 656 patients with MS reported the presence of "speech or other communication problems". Hartelius and associates (62-64) in several studies

examining dysarthria in PwMS have reported a range from 44% to 51% based on patient report and /or speech testing. At pretraining in the current study, dysarthria assessed on a scale ranging from 1 non-vocal to 10 normal speech, 47% (8 of 17) of the PwMS indicated issues with speech. Scores ranged from 7 (obvious speech abnormalities: speech is consistently impaired; affected rate, articulation, and resonance; remains easily understood) to 9 (nominal speech abnormalities: only the patient or spouse notices speech has changed, maintains normal rate and volume). Following training 5 of these 8 subjects increased to a score of 10 (normal speech: patients denies any difficulty speaking, examination demonstrates no abnormality). At detraining 3 of the 5 had reduced scores indicating a return of speech difficulty while 2 maintained their score at detraining. Three subjects increased their score to 9 at posttraining with 2 continuing to improve to 10 at detraining while 1 maintained at the score of 9 at detraining. Scores on two subjects are difficult to explain as one dropped from 10 to 9 then returned to 10 from pretraining to posttraining to detraining, respectively. The second subject had 10 at pretraining and posttraining but dropped to 8 at detraining. The increased score may have resulted from the increased MEP producing a greater subglottal pressure, which permitted the PwMS to speak at a louder level. As discussed above, only one study was found that has used a high intensity vocal therapy, LSVT, in individuals with MS. Loudness of vocalization increased, but quality and intelligibility of the voice did not improve (159). Increased MEP may have permitted the PwMS to speak louder. Anecdotal data from a subject suggests this may have been the case as she reported, "my daughter and husband have stopped telling me to talk louder", and "my daughter says she can hear me when I talk".

Another subject, who had to speak on the phone a great deal of the day for her work, reported "she still had a voice left at the end of work".

Voice Related Quality of Life Measure

Quality of life issues are equally important to examine as objective / measurable data such as the MEP in this study. A general tool assessing health status is the SF-36. Shawaryn and associates (162) using several assessment tools of health-related quality of life (HRQL) in individuals with MS reported that illness intrusiveness was significantly correlated with all indicators of HRQL. These investigators suggested that the results of their study underscore the need to assess MS and its impact more broadly rather than relying on traditional mobility-centered assessments (162). Rothwell and colleagues (148) suggested that clinical trials with PwMS should assess the effect of treatment on the other elements of health status that patients consider important, which are also affected by the disease process, and are more closely related to overall healthy related quality of life. McCabe and McKern (111) reported that people with MS experienced lower levels of quality of life than people from the general population for both the objective and subjective dimensions of all domains (physical health, psychological adjustment, social relationships, environmental adjustment). The individual's perception of MS is also a major factor contributing to quality of life.

The Voice-related Quality of Life measure (V-RQOL) is one of three tools used to assess the impact of impaired voice on quality of life (70, 71). It has been found to be valid and reliable (70). Hogikyan and associates (71) assessed the impact of thyroplasty, a surgical technique used to improve the voice by altering the cartilages of the larynx, had on quality of life through the use of the V-RQOL. Those who had received therapy had

higher overall, social-emotional and physical functioning scores compared to those that did not receive treatment. No study was found that has used the V-RQOL in examining the impact of impaired speech in PwMS. In the current study PwMS reported having more voice related issues that impacted their life than did the healthy controls. An unexpected finding was that 4 of the 14 (28.6%) H subjects reported voice impact on their life. Three of these subjects had MEP, which were on the low side of normal at the initial assessment. Their MEP increased from 30% to 40% at posttraining. Two other healthy subjects also had low side of normal MEP, but reported no impact of voice on their lives. Fifteen of the seventeen PwMS indicated that their voice did effect their life, however the level of impact varied. A closer relationship was found between the physical-functioning and MEP (.454) than between the overall (.391) and the social-emotional (.272) scores compared to MEP. A question on the V-RQOL deals with the ability to speak up. It has been noted that a characteristic of MS dysarthria is diminished loudness (26, 44, 64). A relationship existed between the V-RQOL and its subscales and vowel prolongation at the normal and long SPLs (ranging from .391 to .408, $p< 0.0001$). Similarly, a relationship was found between the V-RQOL and its subscales and WPM at the N and L loudness (ranging from .238 to .410, $p< 0.0001$). Weak to no correlation was found between the V-RQOL and its subscales and the repetition of 'pa' at the N and L loudness. Further study is warranted to assess the value o f the V-RQOL or other voice quality of life scales in PwMS with or without stated voice dysfunction.

Conclusions

In this study we found expiratory muscle weakness in individuals with mild to moderate disability due to MS. EMST was able to strengthen the expiratory as well as the inspiratory muscles of PwMS and healthy controls. The gains in strength were reduced following a detraining period but remained greater than at the baseline assessment. Strengthened expiratory muscles did produce improvements in components of the maximal voluntary cough in that cough airflow increase and remained above baseline following the removal of the stimulus for those with moderate disability due to MS. Training may not have been sufficiently specific to stimulate the motor pattern for cough, therefore no change was seen in the health and Mi group. Those with mild disability may indeed of had greater respiratory involvement of the neural control for the respiratory pump and therefore did not respond to the training stimulus. Strengthened expiratory musculature did improve several acoustic component of speech as well as voice related quality of life issue.

Future questions: 1) Can expiratory muscles be trained in a ballistic manner to simulate the motor pattern that occurs during a cough? 2) Is there a plateau/ceiling in the ability of PwMS for increasing their respiratory muscles? 3) Can the increased expiratory muscle strength be used in conjunction with the LSVT to improve the speech of PwMS?

APPENDIX A

EXPANDED DISABILITY STATUS SCALE (EDSS) AND FUNCTIONAL SYSTEMS SCALE

Expanded Disability Status Scale

Score	Definition
0	Normal neurologic examination (all grade 0 in functional systems (FS): cerebral grade 1 acceptable)
1.0	No disability, minimal signs in one FS (that is, grade 1 excluding cerebral grade 1)
1.5	No disability, minimal signs in more than one FS (more than one grade 1 excluding cerebral grade 1)
2.0	Minimal disability in one FS (one FS grade 2, others 0 or 1)
2.5	Minimal disability in two FS (two FS grade 2, others 0 or 1)
3.0	Moderate disability in one FS (one FS grade 3, others 0 or 1), or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1)
4.0	Fully ambulatory without aid, self-sufficient, up and about 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps. Able to walk 500 m without aid or rest
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively sever disability, usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps. Able to walk 300 m without aid or rest
5.0	Ambulatory without aid or rest for about 200 m; disability severe enough to impair full daily activities (for example, cannot work full day with out special provisions). (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specification for step 4.0).
5.5	Ambulatory without aid or rest for about 100 m; disability severe enough to preclude full daily activities. (Usual FS equivalents are one grade 5 alone, other 0 or 1; or combinations of lesser grades usually exceeding those for step 4.0).
5.0	Intermittent or unilateral constant assistance (cane, crutch, or brace) required to walk about 100 m with or without resting (Usual FS equivalents are combinations with more than two FS grade 3+)
6.5	Constant bilateral assistance (cane, crutch, or brace) required to walk about 20 m

without resting. (Usual FS equivalents are combinations with more than two FS grade 3+)

7.0 Unable to walk beyond about 5 m even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair 12 hours a day. (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely, pyramidal grade 5 alone)

7.5 Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair. (Usual FS equivalents are combinations with more than one FS grade 4+)

8.0 Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms. (Usual FS equivalents are combinations, generally grade 4+ in several systems)

8.5 Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions (Usual FS equivalents are combinations, generally grade 4+ in several systems)

9.0 Helpless in bed; can communicate and eat. (Usual FS equivalents are combinations, generally grade 4+ in several systems)

9.5 Totally helpless in bed; unable to communicate effectively or eat/swallow. (Usual FS equivalents are combinations, almost all grade 4+)

10.0 Death due to MS

Grading of Functional Systems in Multiple Sclerosis

Pyramidal functions

0. Normal
1. Abnormal signs without disability
2. Minimal disability
3. Mild to moderate paraparesis or hemiparesis; severe monoparesis
4. Marked paraparesis or hemiparesis, moderate quadriparesis, or monoplegia
5. Paraplegia, hemiplegia, or marked quadriparesis
6. Quadriplegia

V. Unknown

Cerebellar functions

0. Normal
1. Abnormal signs without disability
2. Mild ataxia
3. Moderate truncal or limb ataxia
4. Severe ataxia, all limbs
5. Unable to perform coordinated movements because of ataxia

V. Unknown

X. Is used throughout after each number when weakness (grade 3 or more on pyramidal) interferes with testing

Brainstem functions

0. Normal
1. Signs Only
2. Moderate nystagmus or other mild disability
3. Severe nystagmus, marked extraocular weakness, or moderate disability of other cranial nerves
4. Marked dysarthria or other marked disability
5. Inability to speak or swallow

V. Unknown

Sensory functions (revised 1982)

0. Normal
1. Vibration or figure-writing decrease only, in one or two limbs
2. Mild decrease in touch or pain or position sense, and/or moderate decrease in vibration in one or two limbs; or vibratory (with or without figure-writing) decrease alone in three or four limbs
3. Moderate decrease in touch or pain or position sense, and/or essentially lost vibration in one or two limbs; or mild decrease in touch or pain and/or moderate decrease in all proprioceptive tests in three or four limbs
4. Marked decrease in touch or pain or loss of proprioception, alone or combined, in one or two limbs; or moderate decrease in touch or pain and/or severe proprioceptive decrease in ore than two limbs essentially) of sensation in one or two limbs; moderate decrease in touch or pain and/or loss of proprioception for most of the
5. Loss (essentially) of sensation in one or two limbs; or moderate decrease in touch or pain and/or loss of propioception for most of the body below the head
6. Sensation essentially lost below the head

V. Unknown

Bowel and bladder functions (revised 1982)

0. Normal
1. Mild urinary hesistancy, urgency, retention
2. Moderate hesistancy, urgency, retention of bowel or bladder, or rare urinary incontinence
3. Frequent urinary incontinence
4. In need of almost constant catheterization
5. Loss of bladder function
6. Loss of bowel and bladder function

V. Unknown

Visual (or optic) functions

0. Normal
1. Scotoma with visual acuity (corrected) better than 20/30
2. Worse eye with scotoma with maximal visual acuity (corrected) of 20/30 to 20/59

3. Worse eye with large scotoma or moderate decrease in fields, but with maximal visual acuity (corrected) of 20/60 to 20/99
4. Worse eye with marked decrease in fields and maximal visual acuity (corrected) of 20/100 to 20/200; grade 3 plus maximal acuity of better eye of 20/60 or less
5. Worse eye with maximal visual acuity (corrected) less than 20/200; grade 4 plus maximal acuity of better eye of 20/60 or less
6. Grade 5 plus maximal visual acuity of better eye of 20/60 or less

V. Unknown

X. Is added to grades 0 to 6 for presence of temporal pallor

Cerebral (or mental) functions

0. Normal
1. Mood alteration only (does not affect Disability Status Scale score)
2. Mild decrease in mentation
3. Moderate decrease in mentation
4. Marked decrease in mentation (chronic brain syndrome – moderate)
5. Dementia or chronic brain syndrome – severe or incompetent

V. Unknown

Other functions

0. None
1. Any other neurologic findings attributed to multiple sclerosis (specify)

V. Unknown

(Kurtzke. Rating neurologic impairment in multiple sclerosis: An expanded disability scale status (EDSS). Neurology 33:1444-1452. 1988.)

APPENDIX B

INDEX OF PULMONARY DYSFUNCTION IN MULTIPLE SCLEROSIS
(Circle one response for each category)

PATIENT'S RATING:		
1. History of difficulty of handling mucus/secretions	no:	1
	yes:	2
2. Cough (patient rates as normal 0r weak/diminished in strength)	normal:	1
	weak:	2
EXAMINER'S RATING:		
3. Strength of patient's cough when asked to cough voluntarily as forcefully as possible	normal:	1
	weak:	2
	very weak/inaudible:	3
4. Value reached when patient counts aloud a single exhalation after maximum inspiratory effort	≥ 30:	1
	20-29:	2
	10-19:	3
	≤ 9:	4
	summed score	_____

(Smeltzer, Lavietes, Troiano, Cook. Testing of an Index of Pulmonary dysfunction in Multiple Sclerosis. Nursing Research. 38(6): 370-375. 1989; Smeltzer, Skurnick, Troiano, Cook, Duran, Lavietes. Respiratory Function in Multiple Sclerosis* Utility of Clinical Assessment of Respiratory Muscle Function. Chest 101(2): 479-484. 1992)

APPENDIX C
THE GRANDFATHER PASSAGE

You wished to know all about my grandfather. Well, he is nearly ninety-three years old. He dresses himself in an ancient black frock coat, usually minus several buttons; yet he still thinks as swiftly as ever. A long flowing beard clings to his chin, giving those who observe him a pronounced feeling of the utmost respect. When he speaks his voice is just a bit cracked and quivers a trifle. Twice each day he plays skillfully and with zest upon our small organ. Except in the winter when the ooze or snow or ice prevents, he slowly takes a short walk in the open air each day. We have often urged him to walk more and smoke less, but he always answers, "Banana Oil!" Grandfather likes to be modern in his language

(Darley, Anderson, & BrowPn Motor Speech Disorders. WB Saunders. Philadelphia PA. 1975; Baken & Orlekoff. Clinical Measurement of Speech & Voice. 2nd Edition. Singular Thomas Learning 2000. p 583).

APPENDIX D

DYSARTHRIA SCALE

Normal Speech Process	
10. Normal Speech	patient denies any difficulty speaking, examination demonstrates no abnormality
9. Nominan speech abnormalities	only the patient or spouse notices speech has changed, maintains normal rate and volume
Detectable speech disturbance	
8. Perceived speech changes	speech changes are noted by others, especially during fatigue or stress; rate of speech remains essentially normal
7. Obvious speech abnormalities	speech is consistently impaired; affected are rate, articulation, and resonance; remains easily understood
Intelligible with repeating	
6. Repeats message on occasion	rate is much slower; repeats specific words in adverse listening situation does not limit complexity or length of messages
5. Frequent repeating required	speech is slow and labored; extensive repetition or a "translator" is commonly used; patient probably limits the complexity or length of messages
Speech and combined with nonvocal communication	
4. Speech plus nonverbal communication	speech is used in response to questions; intelligibility problems need to be resolved by writing or a spokesman
3. Limits speech to one word responses	vocalizes one word responses beyond yes/no; otherwise writes or uses a spokesman; initiates communication non verbally
Loss of speech	
2. Vocalizes for emotional expression	uses vocal inflection to express emotion, affirmation and negation

1. Nonvocal	vocalization is effortful, limited in duration, rarely attempted; may vocalize for crying or pain
X Tracheostomy	

(Yorkston, Mille, Strond. Huntington's Management of Speech and Swallowing in Degenerative Diseases. Communication Skill Builder, division of The Psychological Corporation, Tucson AZ 1995, p 81)

APPENDIX E

VOICE RELATED QUALITY OF LIFE MEASURE

On this paper, you will find a list of possible voice-related problems. Please answer all questions based upon what your **voice** has been like over the past **two weeks**. Considering both how severe the problem is when you get it and how frequently it happens, please rate each item below on how " bad" it is (that is, the **amount** of each problem that you have). Use the following scale for rating the **amount** of the problem:

1 = None, not a problem
2 = A small amount
3 = A moderate (medium) amount
4 = A lot
5 = Problem is as "bad as it can be"

Because of my voice,	How much of a problem is this
1. I have trouble speaking loudly or being heard in noisy situations	1 2 3 4 5
2. I run out of air and need to take frequent breaths when talking	1 2 3 4 5
3. I sometimes do not know what will come out when I begin speaking	1 2 3 4 5
4. I am sometimes anxious or frustrated (because of my voice).	1 2 3 4 5
5. I sometimes get depressed (because of my voice)	1 2 3 4 5
6. I have trouble using the telephone (because of my voice)	1 2 3 4 5
7. I have trouble doing my job or practicing my profession (because of my voice)	1 2 3 4 5
8. I avoid going out socially (because of my voice)	1 2 3 4 5
9. I have to repeat myself to be understood	1 2 3 4 5
10. I have become less outgoing (because of my voice)	1 2 3 4 5

Scoring Algorithm for V-RQOL Measure

VRQOL General Scoring Algorithm:

- 100 – ((raw score - # items in domain or total) x 100)
  ((highest possible raw score - # items))

((50-10)) → 40

Social-Emotional Domain (items 4,5,8,10)

- 100 – ((raw score - 4) x 100)

((20 - 4)) → 16

Physical Functioning Domain (items 1,2,3,6,7,9)

- 100 – ((raw score - 4) x 100)

((30 - 6)) → 24

Total Score (items 1-10)

• Example for Total Score:

If raw score is 30 then:
= 100 – ((20) x 100
((40))

= 100 – (0.5 x 100)
= 100 - 50
= 50 standard score

(Hogikyan & Sethurama. Validation of an instrument to measure voice-related quality of life (V-RQOL) J Voice 1999 13(4): 557-569)

REFERENCE

1. **Addington WR, Stephens RE, Gilliland K, and Rodriguez M.** Assessing the laryngeal cough reflex and the risk of developing pneumonia after stroke. *Arch Phys Med Rehabil* 80: 150-154. 1999.

2. **Addington WR, Stephens RE, Widdicombe JG, Ockey RR, Anderson JW, and Miller SP.** Electrophysiologic latency to the external obliques of the laryngeal cough expiration reflex in humans. *Am J Phys Med Rehabil* 82: 370-373. 2003.

3. **Aisen M, Arlt G, and Foster S.** Diaphragmatic paralysis without bulbar or limb paralysis in multiple sclerosis. *Chest* 98: 499-501. 1990.

4. **Anderson DW, Ellenberg JH, Leventhal CM, Reingold SC, Rodriguez M, and Silberberg DH.** Revised estimate of the prevalence of multiple sclerosis in the United States. *Ann Neurol* 31: 333-336. 1992.

5. **Baker S.** *Expiratory muscle strength training and detraining: effects on speech and cough production* (Dissertation). Gainesville: Florida, 2003.

6. **Baydur A.** Respiratory muscle strength and control of ventilation in patients with neuromuscular disease. *Chest* 99: 330-338. 1991.

7. **Baydur A and Carlson M.** Respiratory mechanics by the passive relaxation technique in conscious healthy adults and patients with restrictive respiratory disorders. *Chest* 105: 1171-1178. 1994.

8. **Beukelman DR, Kraft GH, and Freal J.** Expressive communication disorders in persons with multiple sclerosis: a survey. *Arch Phys Med Rehabil* 66: 675-677. 1985.

9. **Biering-Sorensen F, Lehmann Knudsen J, Schmidt A, Bundgaard A, and Christensen I.** Effect of respiratory training with a mouth-nose-mask in tetraplegics. *Paraplegia* 29: 113-119. 1991.

10. **Black L and Hyatt R.** Maximal respiratory pressures: normal values and relationship to age and sex. *Am Rev Respir Dis* 99: 696-702. 1969.

11. **Black L and Hyatt R.** Maximal Static Respiratory Pressures in Generalized Neuromuscular Disease. *Am Rev Respir Dis* 105: 641-650. 1971.

12. **Boor JW, Johnson RJ, Canales L, and Dunn DP.** Reversible paralysis of automatic respiration in multiple sclerosis. *Arch Neurol* 34: 686-689. 1977.

13. **Bosco C, Komi PV, and Ito A.** Prestretch potentiation of human skeletal muscle during ballistic movement. *Acta Physiol Scand* 111: 135-140. 1981.

14. **Braun N.** Respiratory muscle dysfunction. *Heart Lung* 13: 327-332. 1984.

15. **Buyse B, Demedts M, Meekers J, Vandegaer L, Rochette F, and Kerkhofs L.** Respiratory dysfunction in multiple sclerosis: a prospective analysis of 60 patients. *Eur Respir J* 10: 139-145. 1997.

16. **Campbell AH, Pierce R, and Barter C.** Measurement of airflow resistance and its distribution in the respiratory system. In: *Airway Calibre in Health and Disease: The Pathophysiology of Upper and Lower Airway Narrowing*. New York: Elsevier, 1988, p. 51-64.

17. **Carter JL and Noseworthy JH.** Ventilatory dysfunction in multiple sclerosis. *Clin Chest Med* 15: 693-703. 1994.

18. **Chaudri MB, Hubbard R, Jefferson D, and Kinnear WJ.** Relationship between supramaximal flow during cough and mortality in motor neurone disease. *Eur Respir J* 19: 434-438. 2002.

19. **Coleridge HM and Coleridge JC.** Pulmonary reflexes: neural mechanisms of pulmonary defense. *Annu Rev Physiol* 56: 69-91. 1994.

20. **Colton R and Hirano M.** *Understanding voice problems: A physiological perspective for diagnosis and treatment.* Baltimore: Williams & Wilkins, 1990.

21. **Cooper CB, Trend PS, and Wiles CM.** Severe diaphragm weakness in multiple sclerosis. *Thorax* 40: 633-634. 1985.

22. **Council MS.** *Fatigue and Multiple Sclerosis: Evidence-based Management Strategies for Fatigue in Multiple Sclerosis*: Paralyzed Veterans of America, 1998.

23. **Dail CW.** Respiratory aspects of rehabilitation in neuromuscular conditions. *Arch Phys Med Rehabil* 46: 655-675, 1965.

24. **Darley F, Aronson A, and Brown J.** *Motor Speech Disorder.* Philadelphia, PA, USA: WB Saunders, 1975.

25. **Darley FL, Aronson AE, and Brown JR.** Differential diagnostic patterns of dysarthria. *J Speech Hear Res* 12: 246-269. 1969.

26. **Darley FL, Brown JR, and Goldstein NP.** Dysarthria in multiple sclerosis. *J Speech Hear Res* 15: 229-245. 1972.

27. **Davis FA and Jacobson S.** Altered thermal sensitivity in injured and demyelinated nerve. A possible model of temperature effects in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 34: 551-561. 1971.

28. **Dromey C, Ramig LO, and Johnson AB.** Phonatory and articulatory changes associated with increased vocal intensity in Parkinson disease: a case study. *J Speech Hear Res Aug;* 38: 751-764. 1995.

29. **DuBois AB, Brody AW, Lewis DH, and Burgess BF.** Oscillation mechanics of lungs and chest in man. *J Appl Physiol* 8: 587-594. 1956.

30. **Duchateau J and Enoka RM.** Neural adaptations with chronic activity patterns in able-bodied humans. *Am J Phys Med Rehabil* 81: S17-27. 2002.

31. **Dworkin JP and Hartman DE.** Progressive speech deterioration and dysphagia in amyotrophic lateral sclerosis: case report. *Arch Phys Med Rehabil* 60: 423-425. 1979.

32. **Espir ML and Millac P.** Treatment of paroxysmal disorders in multiple sclerosis with carbamazepine (Tegretol). *J Neurol Neurosurg Psychiatry* 33: 528-531. 1970.

33. **Evans JN.** *An Analysis of the Contribution of Small Airways to Lower Airway Resistance*. Gainesville: Florida, 1976.

34. **Fairbanks G.** *Voice and Articulation Drillbook*. New York: Harper & Row, 1960.

35. **Fisher AB, DuBois AB, and Hyde RW.** Evaluation of the forced oscillation technique for the determination of resistance to breathing. *J Clin Interest* 47: 2045-2057, 1968.

36. **Fiz JA, Aguilar J, Carreras A, Teixido A, Haro M, Rodenstein DO, and Morera J.** Maximum respiratory pressures in trumpet players. *Chest* 104: 1203-1204. 1993.

37. **Flachenecker P, Reiners K, Krauser M, Wolf A, and Toyka K.** Autonomic dysfunction in multiple sclerosis iw related to disease activity and progression of disability. *Multiple Sclerosis* 7: 327-334, 2001.

38. **Foglio K, Clini E, Facchetti D, Vitacca M, Marangoni S, Bonomelli M, and Ambrosino N.** Respiratory muscle function and exercise capacity in multiple sclerosis. *Eur Respir J* 7: 23-28. 1994.

39. **Fontana GA, Pantaleo T, Lavorini F, Boddi V, and Panuccio P.** A noninvasive electromyographic study on threshold and intensity of cough in humans. *Eur Respir J* 10: 983-989. 1997.

40. **Fontana GA, Pantaleo T, Lavorini F, Mutolo D, Polli G, and Pistolesi M.** Coughing in laryngectomized patients. *Am J Respir Crit Care Med* 160: 1578-1584., 1999.

41. **Fragoso CV, Wirz D, and Mashman J.** Establishing a physiological basis to multiple sclerosis- related fatigue: A case report. *Arch Phys Med Rehabil* 76: 583-586, 1995.

42. **Frank NR, Mead J, and Whitenberger JL.** Comparative sensitivity of four methods for measuring changes in respiratory flow resistance in man. *J Applied Physiology* 31: 934-938. 1971.

43. **Freal JE, Kraft GH, and Coryell JK.** Symptomatic fatigue in multiple sclerosis. *Arch Phys Med Rehabil* 65: 135-138. 1984.

44. **FritGerald G.** Multiple Sclerosis: Associated speech and language disorders. *Australian Journal of Human Communication Disorders* 15: 15-33. 1987.

45. **Fry DL, Ebert RV, Stead WW, and Brown CC.** The mechanics of pulmonary ventilation in normal subjects and in patients with emphysema. *Am J Med* 16: 80-97. 1954.

46. **Fujiwara T, Hara Y, and Chino N.** Expiratory function in complete tetraplegics: study of spirometry, maximal expiratory pressure, and muscle activity of pectoralis major and latissimus dorsi muscles. *Am J Phys Med Rehabil* 78: 464-469. 1999.

47. **Garcia Rio F, Prados C, Diez Tejedor E, Diaz Lobato S, Ralvarez-Sala J, Villamor J, and Pino J.** Breathing pattern and central ventilatory drive in mild and moderate generalized myasthenia gravis. *Thorax* 49: 703-706. 1994.

48. **Gibson GJ, Pride NB, Davis JN, and Loh LC.** Pulmonary mechanics in patients with respiratory muscle weakness. *Am Rev Respir Dis* 115: 389-395. 1977.

49. **Giroud M, Guard O, and Dumas R.** cardio-respiratory anomalies in disseminated sclerosis. *Rev Neurol (Paris)* 144: 284-288. 1988.

50. **Gorard DA and Gibberd FB.** Paroxysmal dysarthria and ataxia: associated MRI abnormality. *J Neurol Neurosurg Psychiatry* 52: 1444-1445. 1989.

51. **Gosselink R, Kovacs L, and Decramer M.** Respiratory muscle involvement in multiple sclerosis. *Eur Respir J* 13: 449-454. 1999.

52. **Gosselink R, Kovacs L, Ketelaer P, Carton H, and Decramer M.** Respiratory muscle weakness and respiratory muscle training in severely disabled multiple sclerosis patients. *Arch Phys Med Rehabil* 81: 747-751. 2000.

53. **Gottwald W.** [Paroxysmal syndromes in multiple sclerosis (author's transl)]. *MMW Munch Med Wochenschr* 118: 983-986. 1976.

54. **Grassino AE and Clanton T.** Mechanisms of muscle fatigue. *Monaldi Arch Chest Dis* 48: 94-98. 1993.

55. **Gunal DI, Afsar N, Tanridag T, and Aktan S.** Autonomic dysfunction in multiple sclerosis: correlation with disease-related parameters. *Eur Neurol* 48: 1-5. 2002.

56. **Guthrie T, Kurtzke J, and Berlin F.** Acute respiratory failure in multiple sclerosis and its management. *Ann Internal Medicine* 34: 1197-1203. 1952.

57. **Hakkinen A, Makia K, Hakkinen I, Jappinen L, Hannonen L, and Hannonen P.** Effects of detraining subsequent to strength training on neuromuscular function in patients with inflammatory arthritis. *British Journal of Rheumatology* 36: 1075-1081. 1997.

58. **Häkkinen K, Alen M, Kallinen MA, Newton RU, and Kraemer WJ.** Neuromuscular adaptation during prolonged strength training, detraining and re-strength-training in middle-aged and elderly people. *European Journal of Applied Physiology* 83: 51-62. 2000.

59. **Harik-Khan RI, Wise RA, and Fozard JL.** Determinants of Maximal Inspiratory Pressure. *Am J Respir Crit Care Med,* 158: 1459-1464. 1998.

60. **Harrer G, Harrer H, and Mayr A.** [Autonomic dysfunction in multiple sclerosis (respiratory and cardiac disturbances) (author's transl)]. *Wien Klin Wochenschr* 92: 613-616. 1980.

61. **Hartelius L, Buder EH, and Strand EA.** Long-term phonatory instability in individuals with multiple sclerosis. *J Speech Lang Hear Res* 40: 1056-1072. 1997.

62. **Hartelius L, Nord L, and Buder E.** Acoustic analysis of dysarthria associated with multiple sclerosis. *clinical linguistics & phonetics* 9: 95-120. 1995.

63. **Hartelius L, Runmarker B, and Andersen O.** Prevalence and characteristics of dysarthria in a multiple-sclerosis incidence cohort: relation to neurological data. *Folia Phoniatr Logop* 52: 160-177. 2000.

64. **Hartelius L, Runmarker B, Andersen O, and Nord L.** Temporal speech characteristics of individuals with multiple sclerosis and ataxic dysarthria: 'scanning speech' revisited. *Folia Phoniatr Logop* 52: 228-238. 2000.

65. **Hartelius L and Svensson P.** Speech and swallowing symptoms associated with Parkinson's disease and multiple sclerosis: a survey. *Folia Phoniatr Logop* 46: 9-17. 1994.

66. **Hartman DE.** Neurogenic dysphonia. *Ann Otol Rhinol Laryngol* 93: 57-64. 1984.

67. **Hillel AD, Yorkston K, and Miller RM.** Using phonation time to estimate vital capacity in amyotrophic lateral sclerosis. *Arch Phys Med Rehabil* 70: 618-620. 1989.

68. **Hixon TJ.** *Respiratory Function in Speech and Song*. Boston, MA USA: College-Hill Publication, division of Little, Brown and Company (Inc.). 1987.

69. **Hoffman-Ruddy B.** *Expiratory pressure threshold training in high-risk performers* (Dissertation). Gainesville: University of Florida, 2001.

70. **Hogikyan ND and Sethuraman G.** Validation of an instrument to measure voice-related quality of life (V-RQOL). *J Voice* 13: 557-569. 1999.

71. **Hogikyan ND, Wodchis WP, Terrell JE, Bradford CR, and Esclamado R.** Voice-related quality of life (V-RQOL) following type I thyroplasty for unilateral vocal fold paralysis. *J Voice* 4: 378-386. 2000.

72. **Horsefield K and Cumming G.** Functional consequences of airway morphology. *J Appl Physio* 24: 384-390. 1968.

73. **Howard RS, Wiles CM, Hirsch NP, Loh L, Spencer GT, and Newsom-Davis J.** Respiratory involvement in multiple sclerosis. *Brain* 115: 479-494. 1992.

74. **Hyatt RE.** Expiratory flow limitation. *J Appl Physiol* 55: 1-7. 1983.

75. **Ivey FM, Tracy BL, Lemmer JT, NessAiver M, Metter EJ, Fozard JL, and Hurley BF.** Effects of Strength Training and Detraining on Muscle Quality: Age and Gender Comparisons. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 55: B152-B157. 2000.

76. **Jacome DE.** La toux diabolique: neurogenic tussive crisis. *Postgrad Med J* 61: 515-516. 1985.

77. **Jiang J, O'Mara T, Chen HJ, Stern JI, Vlagos D, and Hanson D.** Aerodynamic measurements of patients with Parkinson's disease. *J Voice* 13: 583-591. 1999.

78. **Jiemsripong K, Hyatt RE, and Offord KP.** Total respiratory resistance by forced oscillation in normal subjects. *Mayo Clin Proc* 51: 553-556. 1976.

79. **Kang S-W and Bach JR.** Maximum insufflation capacity, vital capacity, ad cough flows in neuromuscular disease. *American J Physical Medicine and Research* 79: 222-227. 2000.

80. **Kent JF, Kent RD, Rosenbek JC, Weismer G, Martin R, Sufit R, and Brooks BR.** Quantitative description of the dysarthria in women with amyotrophic lateral sclerosis. *J Speech Hear Res* 35: 723-733. 1992.

81. **Kim MJ and Larson JL.** Ineffective airway clearance and ineffective breathing patterns: theoretical and research base for nursing diagnosis. *Nurs Clin North Am* 22: 125-134. 1987.

82. **Kim MJ, Larson JL, Covey MK, Vitalo CA, Alex CG, and Patel M.** Inspiratory muscle training in patients with chronic obstructive pulmonary disease. *Nurs Res* 42: 356-362. 1993.

83. **Klefbeck B and Nedjad JH.** Effect of inspiratory muscle training in patients with Multiple Sclerosis. *Arch Phys Med Rehabil* 84: 994-999. 2003.

84. **Kraemer WJ and Newton RU.** Training for improved vertical jump. *Sports Science Exchange* 7: 1-12. 1994.

85. **Kurtzke JF.** Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 33: 1444-1452. 1983.

86. **Kurtzke JF, Beebe GW, Nagler B, Auth TL, Kurland LT, and Nefzger MD.** Studies on the natural history of multiple sclerosis. 6. Clinical and laboratory findings at first diagnosis. *Acta Neurol Scand* 48: 19-46. 1972.

87. **Kuwahira I, Kondo T, Ohta Y, and Yamabayashi H.** Acute respiratory failure in multiple sclerosis. *Chest* 97: 246-248. 1990.

88. **Ladefoged P and Leob G.** Preliminary studies on respiratory activity in speech, http://www.humnet.ucla.edu/humnet/linguistic/people/ladefoge/respiration.pdf 1990.

89. **Ladefoged P and McKinney NP.** Loudness, sound pressure, and subglottal pressure in speech. *the Journal of the Acoustical Society of America* 35: 454-460. 1963.

90. **Laghi F and Tobin MJ.** Disorders of the respiratory muscles. *Am J Respir Crit Care Med* 168: 10-48. 2003.

91. **Lands L, Smountas A, Mesiano G, Brosseau L, Shennib H, Charbonneau M, ., and Gauthier R.** Maximal exercise capacity and peripheral skeletal muscle function following lung transplantation. *J Heart Lung Transplant* 18: 113-120. 1999.

92. **Landser FJ, Clement J, and Van de Woestijne KP.** Normal values of total respiratory resistance and reactance determined by forced oscillations: influence of smoking. *Chest* 81: 586-591. 1982.

93. **Laroche CM, Moxham J, and Green M.** Respiratory muscle weakness and fatigue. *Q J Med* 71: 373-397. 1989.

94. **Larson JL, Kim MJ, Sharp JT, and Larson DA.** Inspiratory muscle training with a pressure threshold breathing device in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 138: 689-696. 1988.

95. **Larson M and Kim MJ.** Respiratory muscle training with the incentive spirometer resistive breathing device. *Heart Lung* 13: 341-345. 1984.

96. **Leith DE.** Cough. *Phys Ther* 48: 439-447. 1968.

97. **Leith DE.** Cough. In: *Respiratory Defense Mechanisms, Part II*, edited by Brain JD, Proctor DF and Reid LM. NY: Marcel Dekker, Inc, 1977, p. 545-592.

98. **Leith DE.** The development of cough. *Am Rev Respir Dis* 131: S39-42. 1985.

99. **Leith DE and Bradley M.** Ventilatory muscle strength and endurance training. *J Appl Physiol* 41: 508-516. 1976.

100. **Leith DE, Philip B, Gabel R, Feldman H, and Fencl V.** Ventilatory muscle training and ventilatory control [proceedings]. *Am Rev Respir Dis* 119: 99-100. 1979.

101. **Liaw MY, Lin MC, Cheng PT, Wong MK, and Tang FT.** Resistive inspiratory muscle training: its effectiveness in patients with acute complete cervical cord injury. *Arch Phys Med Rehabil* 81: 752-756. 2000.

102. **Lin VW, Singh H, Chitkara RK, and Perkash I.** Functional magnetic stimulation for restoring cough in patients with tetraplegia. *Arch Phys Med Rehabil* 79: 517-522. 1998.

103. **Loudon RG and Shaw GB.** Mechanics of cough in normal subjects and in patients with obstructive respiratory disease. *Am Rev Respir Dis* 96: 666-677. 1967.

104. **Man WD, Kyroussis D, Fleming TA, Chetta A, Harraf F, Musta N, Rafferty GF, Polkey MI, and Moxham J.** Cough gastric pressure and maximum expiratory mouth pressure in humans. *Am J Respir Crit Care Med* in press, 2003.

105. **Mari F, Matei M, Ceravolo MG, Pisani A, Montesi A, and Provinciali L.** Predictive value of clinical indices in detecting aspiration in patients with neurological disorders. *J Neurol Neurosurg Psychiatry* 63: 456-460. 1997.

106. **Matthews WB.** Paroxysmal symptoms in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 38: 617-623. 1975.

107. **Matthews WB, Read DJ, and Pountney E.** Effect of raising body temperature on visual and somatosensory evoked potentials in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry Mar;* 42: 250-255. 1979.

108. **Mayer N.** Spasticity Pathophysiology: Ciniciophysiologic concepts of spasticity and motor dysfunction in adults with an upper motoneuron lesion. *Muscle Nerve* 20: S1-S13. 1997.

109. **McAllister A and Sundberg J.** Data on subglottal pressure and SPL at varied loudness and pitdch in 8 to 11-year-old children. *TMH-QPSR* 27: 27-36. 1996.

110. **McAlpine D and Compston N.** Some aspects of the natural history of disseminated sclerosis. *Quarterly Journal of Medicine*: 135. 1952.

111. **McCabe MP and McKern S.** Quality of Life and Multiple Sclerosis: Comparison Between People with Multiple Sclerosis and People from the General Population. *Journal of Clinical Psychology in Medical Settings* 9: 287-295. 2002.

112. **McComas AJ.** Human neuromuscular adaptations that accompany changes in activity. *Med Sci Sports Exerc* 26: 1498-1509. 1994.

113. **McFarlin DE and McFarland HF.** Multiple sclerosis (first of two parts). *N Engl J Med* 307: 1183-1188. 1982.

114. **McFarlin DE and McFarland HF.** Multiple sclerosis (second of two parts). *N Engl J Med* 307: 1246-1251. 1982.

115. **Merson RM and Rolnick MI.** Speech-language pathology and dysphagia in multiple sclerosis. *Phys Med Rehabil Clin N Am* 9: 631-641. 1998.

116. **Mier A.** Respiratory muscle weakness. *Respir Med* 84: 351-359. 1990.

117. **Mier A, Brophy C, Moxham J, and Green M.** Repetitive stimulation of phrenic nerves in myasthenia gravis. *Thorax* 47: 640-644. 1992.

118. **Mier A, Brophy C, Wass JA, Besser GM, and Green M.** Reversible respiratory muscle weakness in hyperthyroidism. *Am Rev Respir Dis* 139: 529-533. 1989.

119. **Mier A, Laroche C, Agnew JE, Vora H, Clarke SW, Green M, and Pavia D.** Tracheobronchial clearance in patients with bilateral diaphragmatic weakness. *Am Rev Respir Dis* 142: 545-548. 1990.

120. **Mier-Jedrzejowicz AK, Brophy C, and Green M.** Respiratory muscle function in myasthenia gravis. *Am Rev Respir Dis* 138: 867-873. 1988.

121. **Miley CE and Forster FM.** Paroxysmal signs and symptoms in multiple sclerosis. *Neurology* 24: 458-461. 1974.

122. **Mujika I and Padilla S.** Cardiorespiratory and metabolic characteristics of detraining in humans. *Med Sci Sports Exerc* 33: 413-421. 2001.

123. **Mujika I and Padilla S.** Detraining: loss of training-induced physiological and performance adaptations. Part I: short term insufficient training stimulus. *Sports Med* 30: 79-87. 2000.

124. **Mujika I and Padilla S.** Detraining: loss of training-induced physiological and performance adaptations. Part II: Long term insufficient training stimulus. *Sports Med* 30: 145-154., 2000.

125. **Mujika I and Padilla S.** Muscular characteristics of detraining in humans. *Med Sci Sports Exerc* 33: 1297-1303. 2001.

126. **Murdoch BE, Chenery HJ, Bowler S, and Ingram JC.** Respiratory function in Parkinson's subjects exhibiting a perceptible speech deficit: a kinematic and spirometric analysis. *J Speech Hear Disord* 54: 610-626. 1989.

127. **Netsell R and Kent RD.** Paroxysmal ataxic dysarthria. *J Speech Hear Disord* 41: 93-109. 1976.

128. **Noda S and Umezaki H.** Dysarthria due to loss of voluntary respiration. *Arch Neurol* 39: 132. 1982.

129. **O'Kroy JA and Coast JR.** Effects of flow and resistive training on respiratory muscle endurance and strength. *Respiration* 60: 279-283. 1993.

130. **Olgiati R and di Prampero PE.** [Effect of physical exercise on adaptation to energy expenditure in multiple sclerosis]. *Schweiz Med Wochenschr* 116: 374-377. 1986.

131. **Olgiati R, Girr A, Hugi L, and Haegi V.** Respiratory muscle training in multiple sclerosis: a pilot study. *Schweiz Arch Neurol Psychiatr* 140: 46-50. 1989.

132. **Ostermann PO and Westerberg CE.** Paroxysmal attacks in multiple sclerosis. *Brain* 98: 189-202. 1975.

133. **Peslin R.** Resistance measurements, Forced oscillations and plethysmography. In: *Basics of Respiratory Mechanics and Articial Ventilation*, edited by Milic-Emili J, Lucangelo U, Pesenti A and Zin WA. 1999: springer, 1999, p. 37-57.

134. **Peslin R, Ying Y, Gallina C, and Duvivier C.** Within-breath variations of forced oscillation resistance in healthy subjects. *Eur Respir J* 5: 86-92. 1992.

135. **Pfitzinger P.** What Happens If You Stop Training? http://www.pfitzinger.com/labreports/detraining.shtml 2003.

136. **Popova LM, Avdiunina IA, and Alferova VP.** Respiratory failure in disseminated sclerosis. *Anesteziol Reanimatol*: 59-63. 2000.

137. **Portney LG and Watkins MP.** *Foundations of Clinical Research. Applications to Practice*. Norwalk, Connecticut: Appleton & Lange. 1993.

138. **Proctor D.** *Breathing, Speech, and Song*. New York: Springer-Verlag Wien, 1980.

139. **Ramig LO, Countryman S, O'Brien C, Hoehn M, and Thompson L.** Intensive speech treatment for patients with Parkinson's disease: short-and long-term comparison of two techniques. *Neurology* 47: 1496-1504. 1996.

140. **Ramig LO and Dromey C.** Aerodynamic mechanisms underlying treatment-related changes in vocal intensity in patients with Parkinson disease. *J Speech Hear Res Aug;* 39: 798-807. 1996.

141. **Ramig LO, Sapir S, Countryman S, Pawlas AA, O'Brien C, Hoehn M, and Thompson LL.** Intensive voice treatment (LSVT) for patients with Parkinson's disease: a 2 year follow up. *J Neurol Neurosurg Psychiatry* 71: 493-498. 2001.

142. **Ramig LO, Scherer RC, Klasner ER, Titze IR, and Horii Y.** Acoustic analysis of voice in amyotrophic lateral sclerosis: a longitudinal case study. *J Speech Hear Disord* 55: 2-14. 1990.

143. **Rizvi SS, Ishikawa S, Faling LJ, Schlessinger L, Satia J, and Seckel B.** Defect in automatic respiration in a case of multiple sclerosis. *Am J Med* 56: 433-436. 1974.

144. **Robert D, Pouget J, Giovanni A, Azulay JP, and Triglia JM.** Quantitative voice analysis in the assessment of bulbar involvement in amyotrophic lateral sclerosis. *Acta Otolaryngol* 119: 724-731. 1999.

145. **Rochester D and Arora N.** Respiratory Muscle Failure. *Medical Clinics of North America* 67: 573-97. 1983.

146. **Rogers B, Msall M, and Shucard D.** Hypoxemia during oral feedings in adults with dysphagia and severe neurological disabilities. *Dysphagia* 8: 43-48. 1993.

147. **Romer L and McConnell A.** Specificity and reversibility of inspiratory muscle training. *Med Sci Sports Exerc* 35: 237-244. 2003

148. **Rothwell PM, McDowell Z, Wong CK, and Dorman PJ.** Doctors and patients don't agree: cross sectional study of patients' and doctors' perceptions and assessments of disability in multiple sclerosis. *BMJ* 314: 1580-1583. 1997.

149. **Sant'Ambrogio G.** Afferent pathways for the cough reflex. *Bull Eur Physiopathol Respir* 23: 19s-23s. 1987.

150. **Sant'Ambrogio G.** Coughing: an airway defensive reflex. In: *Pathophysiology of the Gut and Airways*, edited by Andrews and Widdicombe. London. 1993, p. 89-98.

151. **Sant'Ambrogio G and Mathew OP.** Laryngeal receptors and their reflex responses. *Clin Chest Med* 7: 211-222. 1986.

152. **Sant'Ambrogio G, Mathew OP, Fisher JT, and Sant'Ambrogio FB.** Laryngeal receptors responding to transmural pressure, airflow and local muscle activity. *Respir Physiol* 54: 317-330. 1983.

153. **Sapienza C.** Aerodynamic influences in voice production. *Current opinion in Otolaryngology & Head and Neck Surgery* 6: 156-160. 1998.

154. **Sapienza CM, Davenport PW, and Martin AD.** Expiratory muscle training increases pressure support in high school band students. *Journal of Voice* 16: 495-501, 2002.

155. **Sapir S, Ramig LO, Hoyt P, Countryman S, O'Brien C, and Hoehn M.** Speech loudness and quality 12 months after intensive voice treatment (LSVT) for Parkinson's disease: a comparison with an alternative speech treatment. *Folia Phoniatr Logop* 54: 296-303. 2002.

156. **Sawashima M, Niimi S, Horiguchi S, and Yamaguchi H.** Expiratory Lung Pressure: Airflow rate, and vocal intensity: Data on Normal Subjects. In: *Vocal Fold Physiology: Vocal Physiology Voice Production, Mechanisms, and Functions*, edited by Fujimura O. New York: Raven Press, 1988. p. 415-422.

157. **Schorr-Lesnick B, Teirstein AS, Brown LK, and Miller A.** Pulmonary function in singers and wind-instrument players. *Chest* 88: 201-205. 1985.

158. **Scripture EW.** Records of speech in disseminated sclerosis. *Brain* 39: 455-477. 1916.

159. **Seeley EL.** Effectiveness of the Lee Silverman Voice Treatment (LSVT) for Individuals with Multiple Sclerosis: Perceptual Findings. http://ucsub.colorado.edu/~honors/theses/s98/seeley.html 1998.

160. **Senaratne MP, Carroll D, Warren KG, and Kappagoda T.** Evidence for cardiovascular autonomic nerve dysfunction in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 47: 947-952. 1984.

161. **Sharkawi AE, Ramig L, Logemann JA, Pauloski BR, Rademaker AW, Smith CH, Pawlas A, Baum S, and Werner C.** Swallowing and voice effects of Lee Silverman Voice Treatment (LSVT): a pilot study. *J Neurol Neurosurg Psychiatry Jan* 72: 31-36. 2002.

162. **Shawaryn M, Schiaffino K, LaRocca N, and Johnston M.** Determinants of health-related quality of life in multiple sclerosis: the role of illness intrusiveness. *Mult Scler* 8: 310-318. 2002.

163. **Shefner JM, Carter JL, and Krarup C.** Peripheral sensory abnormalities in patients with multiple sclerosis. *Muscle Nerve* 15: 73-76. 1992.

164. **Shefner JM, Mackin GA, and Dawson DM.** Lower motor neuron dysfunction in patients with multiple sclerosis. *Muscle Nerve* 15: 1265-1270. 1992.

165. **Simpson LS.** Effect of increased abdominal muscle strength on forced vital capacity and forced expiratory volume. *Phys Ther* 63: 334-337. 1983.

166. **Smeltzer S.** An index for clinical assessment of pulmonary dysfunction in multiple sclerosis. *N J Nurse* 20: 16, 15. 1990.

167. **Smeltzer SC and Lavietes MH.** Reliability of maximal respiratory pressures in multiple sclerosis. *Chest* 115: 1546-1552. 1999.

168. **Smeltzer SC, Lavietes MH, and Cook SD.** Expiratory training in multiple sclerosis. *Arch Phys Med Rehabil* 77: 909-912. 1996.

169. **Smeltzer SC, Lavietes MH, Troiano R, and Cook SD.** Testing of an Index of Pulmonary Dysfunction in Multiple Sclerosis. *Nurs Res* 38: 370-374. 1989.

170. **Smeltzer SC, Skurnick JH, Troiano R, Cook SD, Duran W, and Lavietes MH.** Respiratory function in multiple sclerosis. Utility of clinical assessment of respiratory muscle function. *Chest* 101: 479-484. 1992.

171. **Smeltzer SC, Utell MJ, Rudick RA, and Herndon RM.** Pulmonary function and dysfunction in multiple sclerosis. *Arch Neurol* 45: 1245-1249. 1988.

172. **Smith Hammond CA, Golstein LB, Zajac DJ, Gray L, P.W. D, and Bolser DC.** Assessment of apiration risk in stroke patients with quantification of voluntary cough. *Neurology* 56: 502-506. 2001.

173. **Sobol BJ.** Test of ventilatory funcitonnot requiring maximal subject effort. II. The measurement of total respiratory impedance. *Ann Rev Respir Dis* 97: 868-879. 1968.

174. **Solomon NP and Hixon TJ.** Speech breathing in Parkinson's disease. *J Speech Hear Res* 36: 294-310. 1993.

175. **Suárez AA, Pessolano FA, Monteiro SG, Ferreyra G, Capria MF, Mesa L, Dubrovshy A, and De Vito EL.** Peak flow and peak cough flow in the evaluation of expiratory muscle weakness and bulbar impairment in patients with neuromuscular diseaase. *American Journal of Physical medicine and rehabilitation* 81: 506-511. 2002.

176. **Syabbalo N.** Respiratory muscle function in patients with neuromuscular disorders and cardiopulmonary diseases. *Int J Clin Pract* 52: 319-329. 1998.

177. **Tantucci C, Massucci M, Piperno R, Betti L, Grassi V, and Sorbini CA.** Control of breathing and respiratory muscle strength in patients with multiple sclerosis. *Chest* 105: 1163-1170. 1994.

178. **Titze IR.** The physics of small-amplitude oscillation of the vocal folds. Apr;. *J Acoust Soc Am* 83: 1536-1552. 1988.

179. **Tobin MJ.** Respiratory muscles in disease. *Clin Chest Med* 9: 263-286., 1988.

180. **Tzeng AC and Bach JR.** Prevention of pulmonary morbidity for patients with neuromuscular disease. *Chest* 118: 1390-1396. 2000.

181. **van Noord JA, Clement J, Cauberghs M, Mertens I, Van de Woestijne KP, and Demedts M.** Total respiratory resistance and reactance in patients with diffuse interstitial lung disease. *Eur Respir J* 2: 846-852. 1989.

182. **Vicken W, Elleker M, and Cosio M.** Determinants of respiratory muscle weakness in stable chronic neuromuscular disorders. *The American Journal of Medine* 82: 53-58. 1987.

183. **Wang TG, Wang YH, Tang FT, Lin KH, and Lien IN.** Resistive inspiratory muscle training in sleep-disordered breathing of traumatic tetraplegia. *Arch Phys Med Rehabil* 83: 491- 496. 2002.

184. **Waxman SG.** Peripheral nerve abnormalities in multiple sclerosis. *Muscle Nerve* 16: 1-5. 1993.

185. **Weiner P, Azgad Y, and Weiner M.** Inspiratory muscle training during treatment with corticosteroids in humans. *Chest* 107: 1041-1044. 1995.

186. **Weiner P, Gross D, Meiner Z, Ganem R, Weiner M, Zamir D, and Rabner M.** Respiratory muscle training in patients with moderate to severe myasthenia gravis. *Can J Neurol Sci* 25: 236-241. 1998.

187. **White DP, Lombard RM, Cadieux RJ, and C.W. Z.** Pharyngeal resistance in normal humans: influence of gender, age, and obesity. *J Appl Physiolo* 58: 365-371. 1985.

188. **White JE, Drinnan MJ, Smithson AJ, Griffiths CJ, and Gibson GJ.** Respiratory muscle activity and oxygenation during sleep in patients with muscle weakness. *Eur Respir J* 8: 807-814. 1995.

189. **Wiens ME, Reimer MA, and Guyn HL.** Music therapy as a treatment method for improving respiratory muscle strength in patients with advanced multiple sclerosis: a pilot study. *Rehabil Nurs* 24: 74-80. 1999.

190. **Winkworth AL, Davis PJ, Ellis E, and Adams RD.** Variability and consistency in speech breathing during reading: lung volumes, speech intensity, and linguistic factors. *J Speech Hear Res* 37: 535-556. 1994.

191. **Winters KM and Snow CM.** Detraining reverses positive effects of exercise on the musculoskeletal system in premenopausal women. *J Bone Miner Res* 15: 2495-2505, 2000.

192. **Yamamoto T, Imai T, and Yamasaki M.** Acute ventilatory failure in multiple sclerosis. *J Neurol Sci* 89: 313-324. 1989.

193. **Yorkston KM, Mille RM, and Strand EA.** *Huntington's Management of Speech and Swallowing in Degenerative Diseases*. Tucson, Arizona: Communication Skill Builder, division of The Psychological Corporation, 1995. p 81.

194. **Yorkston KM, Strand EA, Mille RM, Hillel A, and Smith K.** Speech deterioration in Amyotrophic Lateral Sclerosis: Implications for the timing of intervention. *Journal of Medical Speech-Language Pathology* 1: 35-46. 1993.

195. **Zavalishin IA, Nevskaia OM, and Niiazbekova AS.** [Paroxysmal attacks of dysarthria and ataxia in multiple sclerosis]. *Zh Nevropatol Psikhiatr Im S S Korsakova* 78: 1645-1649. 1978.

196. **Zemlin W.** *Speech and Hearing Science Anatomy and Physiology*. Engelwood Cliffs NJ: Prentice Hall. 1988.

BIOGRAPHICAL SKETCH

Toni Chiara graduated from Santa Rosa Junior College, Santa Rosa, CA. She then headed to the snow country of CA for 2 years. She headed back to college life and completed a BS in Biology at California State College at Chico, Chico, CA. She headed to the high desert of Arizona to work on the Navajo Reservation with the Jesuit Volunteer Corp, Southwest. She spent a year working at St Michael's School, an institution for special needs students. She remained a second year on the reservation working in the St. John County public school in Ganado, AZ, with special needs students, kindergarten to high school. She returned to school, the Physical Therapy Department at University of Southern California. She completed a MSPT a thesis entitled "Effects of Swaddling on the Motor Development of Navajo Children." Following twelve clinical years she again returned to school and completed a MHS through the Department of Physical Therapy at the University of Florida. She was mentored by J. Carlos, Jr. and A.D. Martin, III, completing a master's project entitled "Effect of Cold on Oxygen Consumption, Perceived Exertion and Spasticity during Ambulation in Individuals with MS." Following a 2 year return to the clinic and participation in research at the VAMC Gainesville, FL, working with J. Mueleman, MD, she returned to the University of Florida to pursue a Ph.D. through the rehabilitation science program in the Department. of Physical Therapy within the College of Health Professions, under the mentorship of A.D. Martin, III, PhD, PT. This dissertation is the culmination of studies in exercise, cardiac, and respiratory physiology.

I certify that I have read this and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

A.Daniel Martin III, Chair
Associate Professor of Physical Therapy

I certify that I have read this and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Orit Shechtman
Associate Professor of Occupational Therapy

I certify that I have read this and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Donald Bolser
Associate Professor of Veterinary Medicine

I certify that I have read this and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Christine Sapienza
Associate Professor of Communication Sciences and Disorders

I certify that I have read this and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Paul Davenport
Professor of Veterinary Medicine

This dissertation was submitted to the Graduate Faculty of the College of Health Professions and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

December 2003

Dean College of Health Professions

Dean, Graduate School